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ITS CLINICAL INTERPRETATION

BY

Joseph M. Barker, M.D., F.A.C.P.

Cardiologist, Yater Clinic; Associate Professor of Clinical Medicine, Georgetown University School of Medicine; Director of the Heart Station and Visiting Physician, Georgetown University Hospital; Chief of Cardiology, Gallinger Municipal Hospital; Consulting Cardiologist, Arlington Hospital, Arlington, Virginia.

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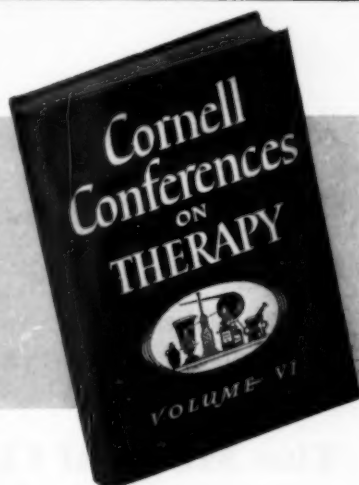
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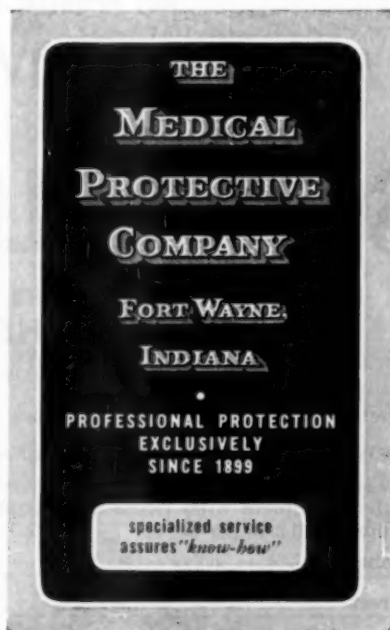
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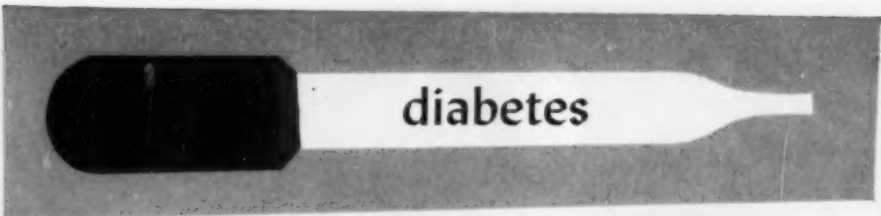
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1. Blotner, H., and Marble, A.: *New England J. Med.* 245:567 (Oct. 11) 1951.

2. Steine, L.: *GP* 8:45 (July) 1953.

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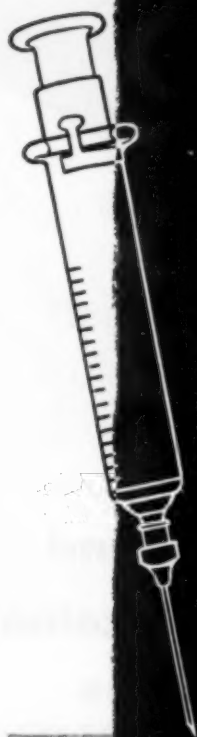


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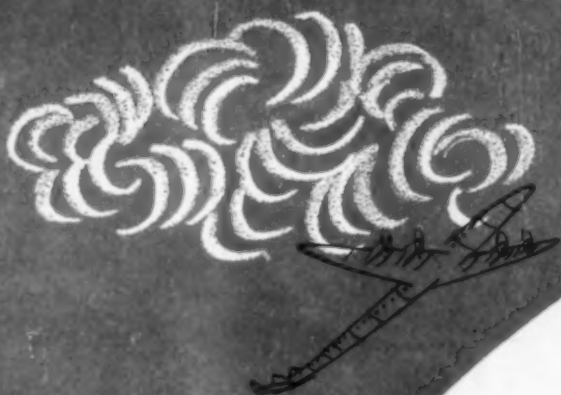
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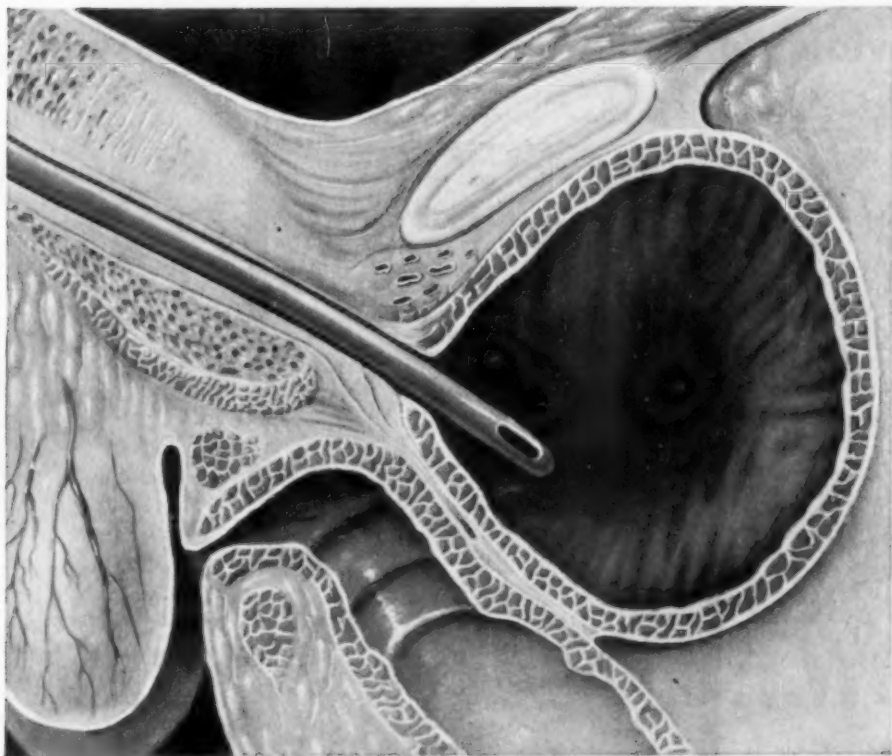
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The "standard maintenance vitamin capsule" and the "therapeutic vitamin capsule" recently recommended in the National Research Council's publication, "Therapeutic Nutrition,"* bring new, authoritative dosage standards into the present complexity of multivitamin formulations and potencies.

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Panalins-T is formulated in accordance with the recommendation* that acutely ill or injured patients receive a therapeutic capsule containing approximately five times the usual daily allowances of B complex vitamins and vitamin C.



*Therapeutic Nutrition, Publication No. 234,
National Research Council.*



The need for two formulations

"The accepted standards of recommended dietary allowances apply to healthy individuals or to certain specific conditions such as pregnancy and lactation. Recent evidence has indicated that these normal allowances may not always be adequate for the sick and injured."*

Standard maintenance capsule for supplementation

"When supplementary vitamins are required, a standard vitamin capsule should be made available. This should contain several vitamins in addition to the six recommended by the National Research Council for normal healthy people."*

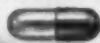
Therapeutic capsule for stress states

"A simple therapeutic capsule would contain approximately five times the usual daily allowances for the various vitamins."*

STANDARDS* maintenance and therapy

PANALINS

N.R.C. STANDARD MAINTENANCE VITAMIN CAPSULE



Conforming precisely
to the N.R.C.
recommendation,[†]
each Panalins
Capsule supplies:

Thiamine.....	2 mg.
Riboflavin.....	2 mg.
Niacinamide.....	20 mg.
Ascorbic acid.....	90 mg.
Calcium pantothenate.....	5 mg.
Pyridoxine hydrochloride.....	0.5 mg.
Folic acid.....	0.25 mg.
Vitamin B ₁₂	2 mcg.
Vitamin A.....	5000 units
Vitamin D.....	400 units

PANALINS-T

N.R.C. STANDARD THERAPEUTIC VITAMIN CAPSULE



Conforming precisely
to the N.R.C.
recommendation,
each Panalins-T
Capsule supplies:

Thiamine.....	10 mg.
Riboflavin.....	10 mg.
Niacinamide.....	100 mg.
Calcium pantothenate.....	20 mg.
Pyridoxine hydrochloride.....	2 mg.
Folic acid.....	1.5 mg.
Ascorbic acid.....	300 mg.
Vitamin B ₁₂	4 mcg.

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A.

MEAD



maalox[®]

gives ulcer relief

without side effects



Gastric hyperacidity is controlled by Maalox-Rorer without constipation or other side effects commonly encountered with antacids. Relief of pain and epigastric distress is prompt and long-lasting. Available in tablets and liquid form.

Suspension Maalox-Rorer contains the hydroxides of Magnesium and Aluminum in colloidal form. The smooth texture and pleasant flavor make it highly acceptable, even with prolonged use.

Supplied: in 355 cc. (12 fluid ounce) bottles. Also in bottles of 100 tablets. (Each Maalox tablet is equivalent to 1 fluidram of Suspension Maalox.)

Samples will be sent promptly on request.

WILLIAM H. RORER, INC.

Drexel Bldg., Independence Square
Philadelphia 6, Pa.

for routine salicylate administration

Armyl is therapeutically different*

the difference results from
50 mg. of ascorbic acid
per tablet

+sodium salicylate 0.3 Gm.

+sodium para-aminobenzoate 0.3 Gm.

***Helps protect the patient on salicylate therapy**

- provides higher plasma salicylate levels with lower salicylate dosage
- provides against vitamin C depletion due to urinary loss
- provides the antihemorrhagic protection of vitamin C during prolonged salicylate therapy

For your prescribing convenience:

Armyl—Armyl with $\frac{1}{8}$ gr. Phenobarbital.

Also available for patients on sodium restriction:

Armyl Sodium-Free—Armyl Sodium-Free with $\frac{1}{8}$ gr. Phenobarbital.

Supplied in bottles of 100.



THE ARMOUR LABORATORIES

A DIVISION OF ARMOUR AND COMPANY • CHICAGO 11, ILLINOIS

In tetany

LATENT OR MANIFEST...

gradual, sustained rise
of blood calcium level

HYTAKEROL®

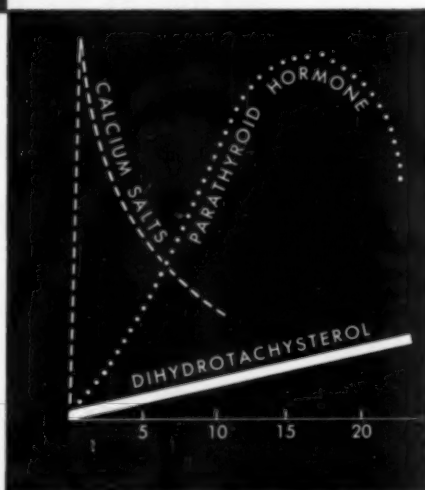
BRAND OF DIHYDROTACHYSTEROL



"DIHYDROTACHYSTEROL...

has proved to be the most valuable remedy for the control of chronic hypoparathyroidism and by its use patients may be kept free of the symptoms of tetany as well as of the trophic manifestations of chronic hypocalcemia."*

In acute hypoparathyroidism the simultaneous use of calcium salts (intravenously), parathyroid hormone (subcutaneously) and Hytakeral (orally) is advised in the beginning, the blood calcium level being then maintained by oral administration of dihydrotachysterol and calcium salts.



Blood calcium response to various forms of therapy. Note slow, steady rise following dihydrotachysterol orally.*

Winthrop-Stearns INC.
NEW YORK 18, N. Y. WINDSOR, ONT.

*Grellman, A.: *Essentials of Endocrinology*. Philadelphia, J. B. Lippincott Co., 1947, 2d ed., p. 267, 269.

Hytakerol, trademark reg. U. S. and Canada, brand of dihydrotachysterol

COMPARISON OF CRYPTENAMINE WITH PROTOVERATRINE AND THREE OTHER VERATRUM ALKALOID PREPARATIONS		
DRUG	Emetic: Therapeutic Ratio	Therapeutic Index
Cryptenamine—Irwin-Neisler	4:1	125
Protoveratrine A & B	1:1	20
Commercial Veratrum Alkaloid Preparation A	1.2:1	40
Commercial Veratrum Alkaloid Preparation B	1:1	
Commercial Veratrum Alkaloid Preparation C	1:1	

*Another *
reason why*



THERE IS NO SAFER PREPARATION FOR THE TREATMENT OF HYPERTENSION

Each tabule contains:

Whole-powdered *Veratrum viride* (containing *Cryptenamine*) . . . 40 C.S.R.† Units

Sodium Nitrite . . . 1 grain

Phenobarbital . . . ¼ grain

Carotid Sinus Reflex

Supplied: Bottles of 100, 500, 1000.

Veratrite® brings your hypertensive patients the best therapeutic benefits of Veratrum, since it provides Cryptenamine * the newly isolated, broader safety-ratio Veratrum alkaloid developed through Irwin-Neisler research.

Sustained control of blood pressure, with minimum side reactions and maximum safety, is the significant contribution of Veratrite to the long-term management of hypertension.

Veratrite

IRWIN, NEISLER & COMPANY • DECATUR, ILLINOIS

What about Cobalt?

—in anemia—

Q. Why is Roncovite* effective in anemias of bone marrow depression due to infection or disease?

A. Because cobalt is the only agent known which, by stimulating erythropoiesis, will cause the hemopoietic system to utilize the iron already available to it.

Q. Why use cobalt in iron-deficiency anemia—isn't iron alone adequate?

A. Roncovite is preferentially indicated in ALL forms of "secondary" or iron-deficiency anemia for the following reasons:

Many so-called iron-deficiency anemias are in reality a combination of an iron-deficiency and an inhibition of hemopoiesis *resulting from long continued extra drain* on the bone marrow.

With iron alone,¹ therefore, a complete clinical response is often difficult or impossible to obtain—only very small gains or poor responses being frequently reported in "low-grade anemias."

Roncovite, by providing the added bone marrow (red cell) stimulant action of cobalt, will supply that added extra "push" to mobilize iron reserves, produce a faster response, greatly superior erythropoiesis and up to fourfold increases in the utilization of iron.²

Q. Why is iron present in Roncovite?

A. The increased hemopoiesis from the specific bone marrow stimulant action of cobalt often creates a need for additional iron to make hemoglobin for the new red cells—Roncovite provides iron to fill this need and to maintain iron reserves.

Q. Can I be sure that cobalt is safe for routine use?

A. Cobalt is an essential element with a low order of toxicity—no greater than that of iron. A cobalt chloride dosage of as high as

1200 mg. per day, in divided doses, has produced no severe toxic effects even if continued for six weeks.³ This is equivalent to a daily dosage of over 80 Roncovite tablets.

Q. Is cobalt cumulative?

- A. No—extensive pharmacological investigation proves that cobalt is rapidly and almost completely excreted via the urine⁴ so that there is little if any cumulative effect even after periods exceeding 100 days of continuous parenteral use. The body shows no significant amounts of cobalt 48 hours after the last dose.⁴

Q. Is the improvement with Roncovite noticeably rapid?

- A. Yes—the patient often voluntarily reports an increased sense of well-being within a few days—as reported by documented clinical evidence.

Roncovite is not indicated in pernicious or megaloblastic anemia.

HOW SUPPLIED:

Roncovite Tablets—enteric coated, red, each contains cobalt chloride, 15 mg.; exsiccated ferrous sulfate, 0.2 Gm.; bottles of 100.

Roncovite Drops—each 0.6 cc. contains cobalt chloride, 40 mg.; ferrous sulfate, 75 mg.; bottles of 15 cc. with calibrated dropper.

RONCOVITE

The First True Hematopoietic Stimulant

1. Cass, L. J.; Frederick, W. S., and DiGregorio, S.: *Journal-Lancet* 51:73 (1953).

2. Rohn, R. J., and Bond, W. H. Jr.: *Lancet* 73:301 (1953).

3. Berk, W., et al.: *New England J. M.* 240:754 (May) 1949.

4. Berlin, N. I.: *J. Biol. Chem.* 187:41 (1950).

*The original Cobalt-Iron Product.

LLOYD BROTHERS, Inc.
CINCINNATI 3, OHIO

Eminent Economist

...dietary dub

HE KNOWS ECONOMY. Even economizes on his vitamin intake.

Eventually, he'll be studying a corrected diet and looking to you for a potent B-complex supplement like SUR-BEX or SUR-BEX with Vitamin C.

Each compressed, triple-coated tablet provides six B vitamins. Also, liver fraction and brewer's yeast. SUR-BEX with C adds 150 mg. of ascorbic acid.

No trace of offensive liver odor—only the pleasant aroma of the vanilla-flavored sugar coating. Daily therapeutic dose is one easy-to-swallow tablet. Two or more for severe deficiencies. In bottles of 100, 500 and 1000. **Abbott**



EACH SUR-BEX TABLET CONTAINS:

Thiamine mononitrate 6 mg.
 Riboflavin 6 mg.
 Nicotinamide 30 mg.
 Pyridoxine hydrochloride 1 mg.
 Vitamin B₁₂ 2 mcg.
 (as vitamin B₁₂ concentrate)
 Pantothenic acid 10 mg.
 (as calcium pantothenate)
 Liver fraction 2, N.F. . 0.3 Gm. (5 grs.)
 Brewer's yeast, dried
 0.15 Gm. (2½ grs.)

SUR-BEX WITH VITAMIN C contains 150 mg. of ascorbic acid in addition to the vitamin B complex factors.

prescribe

SUR-BEX[®]

(ABBOTT'S VITAMIN B COMPLEX TABLETS)

or **SUR-BEX with C**

Have you tasted Meritene Doctor?

One taste tells the story. Here is the high protein nourishment patients will delight in drinking... the sure route to *extra* nutrition whenever required, for all ages.

Let us send *you* a one pound can for your own taste-test.



**HIGH PROTEIN Supplementation
and it tastes good**

MERITENE vs. EGGNOG Nutritive Value Comparison

	EGGNOG	MERITENE MILK SHAKE
Protein.....	12.5 gm.	15.8 gm.
Fat.....	12.6 gm.	8 gm.
Carbohydrate..	17.7 gm.	25.5 gm.
Calcium.....	.24 gm.	.5 gm.
Phosphorus....	.27 gm.	.4 gm.
Iron.....	1.5 mg.	4.4 mg.
Vitamin A.....	843 I.U.	1745 I.U.
Thiamine.....	.12 mg.	.7 mg.
Riboflavin.....	.45 mg.	1.6 mg.
Ascorbic Acid...	2.0 mg.	26.4 mg.
Cholesterol....	288 mg.	21 mg.
Calories.....	233	237

Eggnog nutritive values from "Food Values of Portions Commonly Used." Bowes & Church, 1951.



INSTITUTIONAL SIZE PRICE
(in 100 pound quantities)—89¢ per pound

In the management of medical and surgical convalescence, debilitating diseases, geriatric nutritional imbalance...you immediately seek to increase the patient's protein intake.

More and more physicians are finding the answer in MERITENE—the fortified whole protein supplement that patients *like to take*. Its good taste assures that.

Therapeutic values abound in a Meritene Milk Shake: high quality protein without the burden of bulk...more of all other important vitamins and minerals than in an equal amount of Eggnog. Yet Meritene Milk Shakes cost *less*. Write for a full one pound can... or

MAIL THIS COUPON

THE DIETENE COMPANY

3017 Fourth Avenue South, Minneapolis 8, Minnesota

I am interested in becoming more familiar with MERITENE. Please send me FREE a one pound can so that I can try it.

NAME _____ M.D.

ADDRESS _____

CITY _____ ZONE _____ STATE _____

Taste Toppers . . . for all ages



that's what physicians and patients alike call these two favorite dosage forms of Terramycin because of their unsurpassed good taste. They're nonalcoholic — a treat for patients of all ages, with their pleasant raspberry taste. And they're often the dosage forms of first choice for infants, children and adults of all ages.

Terramycin®

BRAND OF OXYTETRACYCLINE



Pediatric Drops

Each cc. contains 100 mg. of pure crystalline Terramycin. Supplied in 10 cc. bottles with special dropper calibrated at 25 mg. and 50 mg. May be administered directly or mixed with nonacidulated foods and liquids. Economical 1.0 gram size often provides the *total dose* required for treatment of infections of average severity in infants.

Supplied: Bottles of 1.0 Gm. *



Oral Suspension (Flavored)

Each 5 cc. teaspoonful contains 250 mg. of pure crystalline Terramycin. Effective against gram-positive and gram-negative bacteria, including the important coli-aerogenes group, rickettsiae, certain large viruses and protozoa.

Supplied: Bottles of 1.5 Gm.



PFIZER LABORATORIES, Brooklyn 6, N. Y., Division, Chas. Pfizer & Co., Inc.

in the treatment of Hypertension**Effectively**

**mannitol hexanitate exerts
vasodilator action and
persistent relaxation of
smooth muscle**

New and Nonofficial Remedies: A.M.A. Council on
Pharmacy and Chemistry, J. B. Lippincott, p. 243, 1953.

Safely

**fewer side effects
with mannitol hexanitate
... greater percentage fall
in blood pressure**

N. Y. Physician 31:20 (Jan.) 1949.

Economically

**combined medication
that provides simultaneously:**

vasodilatation (mannitol hexanitate)
diuresis (theophylline)
sedation (phenobarbital)
capillary protection (ascorbic acid + rutin)

Semhyten[®]

BRINGS THE PRESSURE DOWN SLOWLY



SAFELY

Complete Medication for the Hypertensive

Each Semhyten Capsule contains:	Phenobarbital . . . ¼ gr. (15 mg.)
Mannitol Hexanitate . . . ½ gr. (30 mg.)	Rutin 10 mg.
Theophylline 1½ gr. (0.1 Gm.)	Ascorbic Acid 15 mg.

Supplied: In bottles of 100, 500 and 1000 pink-top capsules.

The S. E. MASSENGILL Company • Bristol, Tennessee

*A NEW
BROAD-SPECTRUM
ANTIBIOTIC*

ACHRO

Please Mention this Journal when writing to Advertisers

More Rapid Absorption**Increased Toleration****Greater Stability**

ACHROMYCIN, a new broad-spectrum antibiotic developed by the Lederle research team, has demonstrated greater effectiveness in clinical trials with the advantages of more rapid absorption, quicker diffusion in tissue and body fluids, and increased stability resulting in prolonged high blood levels.

ACHROMYCIN exhibits a broad range

of activity against beta hemolytic streptococcal infections, *E. coli* infections (including urinary tract infections, peritonitis, abscesses), meningococcal, staphylococcal, pneumococcal and gonococcal infections, otitis media and mastoiditis, acute bronchitis and bronchiolitis, and certain mixed infections.

ACHROMYCIN is now available in 250 mg., 100 mg., and 50 mg. capsules, SPERSOIDS® 50 mg. per teaspoonful (3.0 Gm.), Intravenous 500 mg., 250 mg. and 100 mg. Other dose forms will become available as rapidly as research permits.



LEDERLE LABORATORIES DIVISION

AMERICAN Cyanamid COMPANY

30 Rockefeller Plaza, New York 20, N.Y.

MYCIN®

TETRACYCLINE CAPSULES LEDERLE



LONALAC MAKES THE DIFFERENCE

IN LOW SODIUM DIETS

—with Lonalac...

adequate protein

Rx

200 mg. sodium diet
Meat, 1 serving
Egg, 1
Low sodium bread
Cereal
Vegetables
Fruits

Average protein —
50 Gm.
Average sodium —
180 mg.

Rx

200 mg. sodium diet
Meat, 1 serving
Egg, 1
Low sodium bread
Cereal
Vegetables
Fruits

Lonalac — 1 quart
liquefied — to be
used like milk

Average protein —
80 Gm.
Average sodium —
200 mg.

—without Lonalac...

inadequate protein

Nutritionally similar to whole milk but with negligible sodium content, Lonalac solves the problem created by the high sodium content of the usual protein foods.

When sodium intake must be sharply restricted, protein deficiency is seriously threatened... since meat and eggs can be used only in small quantities and milk, with its still higher sodium content, usually must be eliminated.

With Lonalac supplying the protein equivalent of milk, the patient's nutritional needs can be generously met, even on a 200 mg. sodium diet.

Lonalac is used just as milk is used, as a beverage and in soups, muffins, desserts, etc. It permits varied and appetizing meals that encourage patients to adhere to a low sodium regimen.

Lonalac is virtually free of cholesterol.

Lonalac is supplied in 1 pound and economical 4 pound cans. Low sodium diet outlines suitable for use by patients are available on request.

Lonalac

The low sodium, high protein food

MEAD JOHNSON & COMPANY • EVANSVILLE, INDIANA, U.S.A.

MEAD

Please Mention this Journal when writing to Advertisers

Upjohn

oral
estrogen-progesterone
effective in
menstrual disturbances:

Each scored tablet contains:

Estrogenic Substances* .. 1 mg.
(10,000 I.U.)

Progesterone 30 mg.

**Naturally-occurring equine estrogens (consisting primarily of estrone, with small amounts of equilin and equilinenin, and possible traces of estradiol) physiologically equivalent to 1 mg. of estrone.*

Available in bottles of 15 tablets.

The Upjohn Company, Kalamazoo, Michigan

Cyclogesterin
TRADEMARK, REG. U.S. PAT. OFF.
tablets



NOW

A safer tranquilizer-antihypertensive

Serpasil^{T.M.}

(PEDIOPHIL CIBA)

A pure crystalline alkaloid of Rauwolfia serpentina

Serpasil, a pure, crystalline, single alkaloid of *Rauwolfia serpentina*, produces mild, gradual, sustained lowering of blood pressure without undesired effects from unknown alkaloids of the whole root. Other advantages:

- Effective alone or in combination with other antihypertensive agents.
- Uniform potency.
- Predictable therapeutic results.
- No tolerance developed, or toxic effects reported; no contraindications; no serious side effects.

Virtually every hypertensive patient may be treated with **Serpasil** therapy. Prescribe this safer tranquilizer-antihypertensive now. Available at all prescription pharmacies.

Serpasil Tablets, 0.25 mg. and 0.1 mg., bottles of 100.

Ciba Summit, New Jersey

2 / 1057M

For
the patient
in pain —

Levo-Dromoran Tartrate 'Roche'

... a new form of synthetic narcotic...
less likely to produce constipation or
nausea than morphine... usually longer
acting than morphine... especially for
intractable pain. Levo-Dromoran®--
brand of levorphan.

Gantrisin 'Roche' —
a single, soluble,
wide-spectrum
sulfonamide —

Gantrisin 'Roche' is especially
soluble at the pH of the kidneys.
That's why it is so well tolerated...
does not cause renal blocking... does
not require alkalies. Produces high
plasma as well as high urine levels.
Over 150 references to Gantrisin® in
recent literature.

THESODATE

THE ORIGINAL ENTERIC-COATED TABLET
OF THEOBROMINE SODIUM ACETATE

provides
**EFFECTIVE
WELL-TOLERATED
PROLONGED
VASO-DILATION**



REPEATEDLY SHOWN and proven by objective tests on human subjects¹ — this is one of the most effective of all the commonly known Xanthine derivatives. Because of the enteric coating it may be used with marked freedom from the gastric distress characteristic of ordinary Xanthine therapy. Thus THESODATE, with its reasonable prescription price also, enjoys a greater patient acceptability.

Available: In bottles of 100, 500, 1000.

TABLETS THESODATE

* (7½ gr.) 0.5 Gm. * (3¾ gr.) 0.25 Gm.

THESODATE WITH PHENOBARBITAL

* (7½ gr.) 0.5 Gm. with (½ gr.) 30 mg.

(7½ gr.) 0.5 Gm. with (¼ gr.) 15 mg.

* (3¾ gr.) 0.25 Gm. with (¼ gr.) 15 mg.

THESODATE WITH POTASSIUM IODIDE

(5 gr.) 0.3 Gm. with (2 gr.) 0.12 Gm.

THESODATE, POTASSIUM IODIDE WITH PHENOBARBITAL

(5 gr.) 0.3 Gm., (2 gr.) 0.12 Gm. with (¼ gr.) 15 mg.

* In capsule form also, bottles of 25 and 100.

1. Riseman, J. E. F. and Brown, M. G. Arch. Int. Med. 60: 100, 1937.

2. Brown, M. G. and Riseman, J. E. F. JAMA 109: 256, 1937.

3. Riseman, J. E. F. N. E. J. Med. 229: 670, 1943.

For samples just send your Rx blank marked — 7TH1



BREWER & COMPANY, INC. WORCESTER 8, MASSACHUSETTS U.S.A.

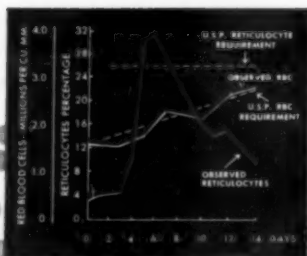
in
**CORONARY
ARTERY
DISEASE**

Why **BIOPAR** is an effective oral replacement for injectable vitamin B₁₂

With Biopar, effective absorption of vitamin B₁₂ through the intestinal barrier is assured—even in the presence of partial or complete achlorhydria.

Absorption is assured because the intrinsic factor in Biopar performs the functions ascribed to the Intrinsic Factor of Castle.

Biopar's completely new intrinsic factor is another pioneering hematologic advance made by The Armour Laboratories.



BIOPAR®

Each Biopar tablet contains:
Crystalline Vitamin B₁₂ U.S.P. . . . 6 mcg.
Intrinsic Factor 30 mg.

Supplied: Bottles of 30 tablets.



Biopar produces prompt, positive reticulocyte and erythrocyte response in patients with pernicious anemia.

When you give Biopar, you can be sure that the patient is getting the full benefits of oral vitamin B₁₂ therapy. Biopar is an effective method of administering vitamin B₁₂ . . . the patient is spared the discomfort of injection.



THE ARMOUR LABORATORIES

A DIVISION OF ARMOUR AND COMPANY • CHICAGO 33, ILLINOIS



AMPHOJEL®
ALUMINUM HYDROXIDE GEL
WYETH'S ALUMINA GEL

In uncomplicated
PEPTIC ULCER
prompt healing may
be anticipated when
acid and pepsin
corrosion are halted.
"Double-Gel action" of
Amphojel provides
both local physical
protection and gentle
sustained antacid effect.

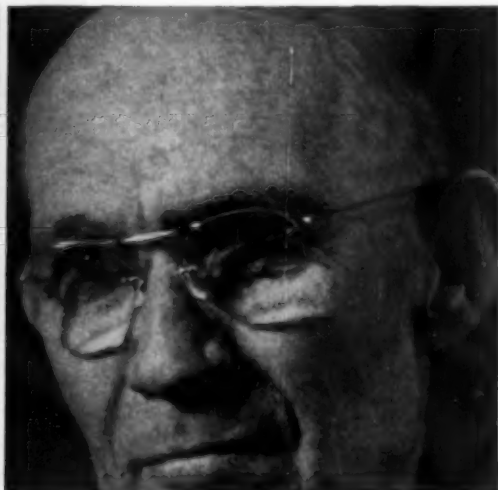


Philadelphia 2, Pa.

Please Mention this Journal when writing to Advertisers

DEXAMYL* relieved...

... anxiety in a tired businessman



Patient T. H. complained of "fatigue and early morning weariness . . . refused to stop work and rest . . ."

"The relief that 'Dexamyl' brought in this case is incalculable." It relieved his anxiety about his work and helped him through the days he felt "low".

(Case-history excerpts from the files of a general practitioner, unposed photographs taken during office visit.)

Each tablet provides the synergistic action of two mood-ameliorating components: Dexedrine* Sulfate (dextro-amphetamine sulfate, S.K.F.), 5 mg.; amobarbital (Lilly), $\frac{1}{2}$ gr. (32 mg.). Each teaspoonful (5 cc.) of the elixir is equivalent to one tablet.

*T.M. Reg. U.S. Pat. Off.

... despondency from the "dread of advancing years"



Patient W. F.'s "emotional cyclones, her tears and giggles, her hopelessness were products of her brooding unhappiness when alone."

"'Dexamyl' gave her a smoother existence, alleviating her moodiness and lessening her storms."

'DEXAMYL' tablets and elixir

—relieves both anxiety and depression

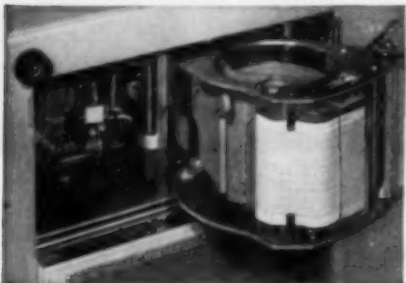
—promotes a feeling of composure

Smith, Kline & French Laboratories, Philadelphia

NEW GE Cardioscribe offers 5 big advantages



- 1 Self-stabilized** — No more undiagnosible tracings due to line-voltage fluctuations, and stabilization time between leads has been cut.



- 2 Improved paper drive** — Operates independent of stylus, is easily loaded, can be quickly adjusted for correct paper tension.



- 4 New design puts controls at your finger-tips.** Dual, recessed, hinged tops cover controls — support no weight when unit is carried.

Here's General Electric's answer to your demands for faster, easier, more accurate electrocardiography. It's the *all-new* GE Cardioscribe. Take a look at the five outstanding features shown here. But they're only part of the story! For full information, see your GE x-ray representative, or write X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin, for Pub. M-1.

GENERAL  ELECTRIC



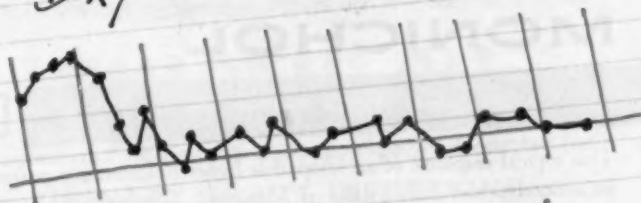
- 3 Exclusive chest selector switch** — You can connect individual chest electrodes and check six positions — all in just 10 minutes!



- 5 30-lead selection** — Once all electrodes are positioned on the patient you can get 30 leads by simply rotating the selector switches.

Please Mention this Journal when writing to Advertisers

Dx/ Pneumonia



R/ Terramycin

brand of oxytetracycline

an antibiotic
of choice

When the diagnosis is pneumonia, Terramycin therapy usually brings quick results because this broad-spectrum antibiotic is equally effective against coccal, Friedländer's and atypical virus pneumonia.

"After the administration of Terramycin, 59 of the [60] patients... improved rapidly with almost complete defervescence within twenty-four hours."

Given in the recommended daily adult dose of 250 to 500 mg. q. 6 h., Terramycin is exceptionally well tolerated.

"There were no toxic manifestations from this antibiotic.... No nausea or vomiting was noted. No patient developed leukopenia."

Even cases that resisted previous treatment with other agents frequently show a gratifying response to Terramycin therapy.

"A case of staphylococcal pneumonia, complicated by tension pneumothorax which had shown no response to [another antibiotic], made a rapid, complete recovery on a dosage of 15 mg. per lb."

1. Knight, V.: New York State J. Med. 50:2173 (Sept. 15) 1950.
2. Potterfield, T. G., and Starkweather, G. A.: J. Philadelphia Gen. Hosp. 2:6 (Jan.) 1951.
3. Swift, P. N.: Proc. Roy. Soc. Med. 44:1066 (Dec.) 1951.



Pfizer

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

the realization of a hope . . .

a new physio-chemical complex that consistently and significantly reduces elevated serum cholesterol levels.

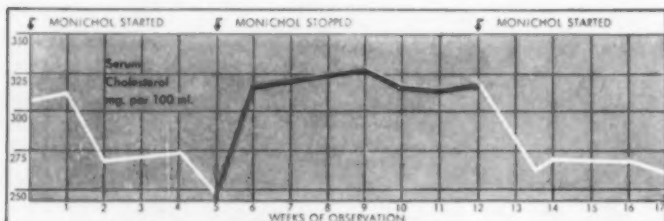
MONICHOL*



This typical response of an idiopathic hypercholesteremic patient to an uninterrupted daily intake of Monichol — an entirely non-toxic medication — shows a significant drop from 306 mg. to 240 mg. per 100 ml. of serum cholesterol after five weeks of medication.†

The investigators† stress the need for continued administration of Monichol because idiopathic or familial hypercholesteremia is most probably an *inborn error of metabolism*.

Uninterrupted Daily Intake of Monichol
Essential in the Management of Hypercholesteremia



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†Sherber, D. A., and Levites, M. M.: Hypercholesteremia. Effect on Cholesterol Metabolism of a Polysorbate 80-Choline-Inositol Complex (MONICHOL) J.A.M.A. 152:682 (June 20) 1953.

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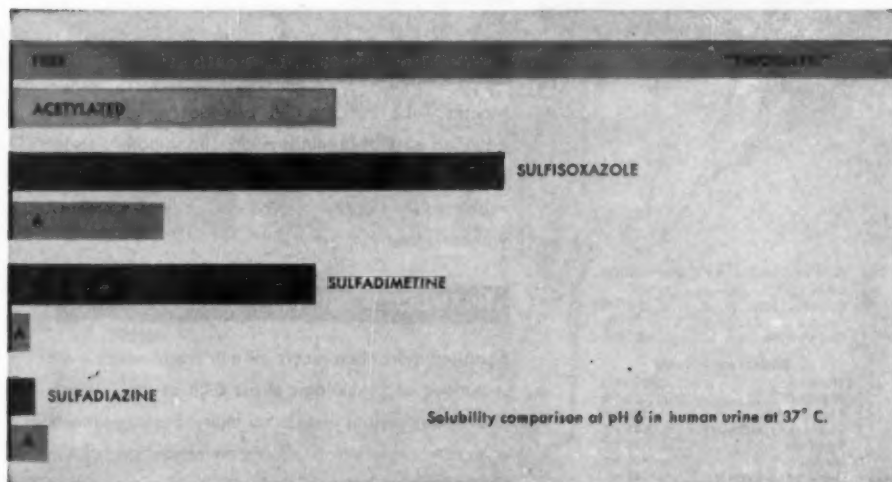
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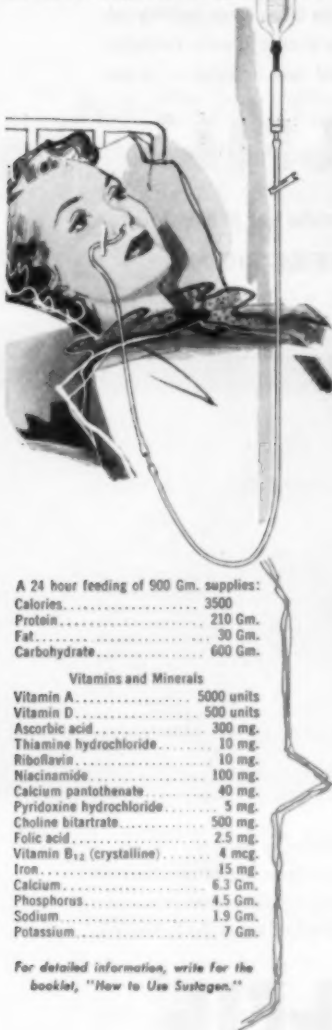
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Escher, G. C., et al.: Clinical Research Proceedings 1:51 (Apr.) 1959.

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1. HUFFORD, A. R.: ICHN. STATE MED. SOC. 45:1308, 1950.

2. RICHARDY, G. AND BROWNE, D.: SOU. MED. J. 45:1139, 1952.

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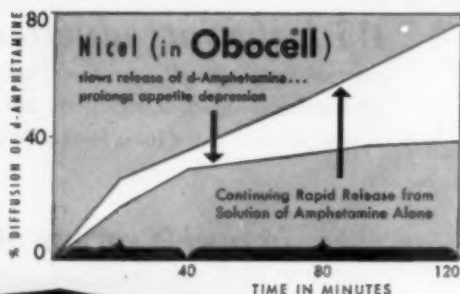
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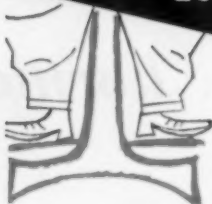
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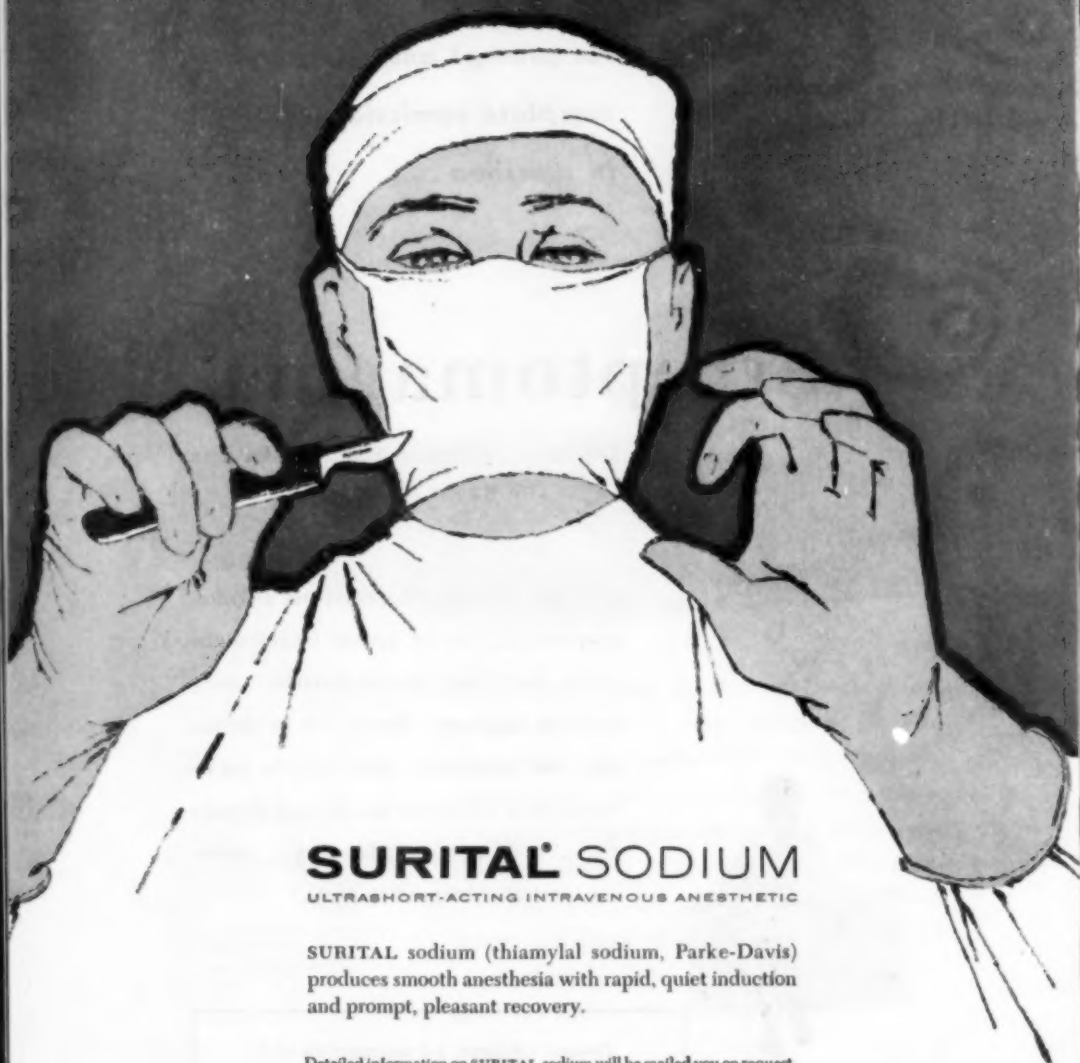


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†Editorial, J. Allergy 23: 279-280, 1952.



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Herrold, R. D.: South. Clin. North America 30:61, 1950.

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(1) Burns, J. J., and others: J. Pharmacol. & Exper. Therap. 196:373, 1952. (2) Byrnes, C. S., and Ornstein, H. B.: New York State J. Med. 53:676 (Mar. 15) 1953. (3) Currie, J. P.: Lancet 2:15 (July 5) 1952. (4) Davies, H. R.; Bartor, R. W.; Gee, A., and Hiron, C.: Brit. M. J. 2:1092 (Dec. 27) 1952. (5) Delfel, N. E., and Griffin, A. C.: Stanford M. Bull. 2:65, 1953. (6) Domenjot, R.: Federation Proc. 11:339, 1953. (7) Domenjot, R.: Internat. Rev. Med. 165:467, 1952. (8) Goldstein, E.: J. Oklahoma M. A. 46:27, 1953. (9) Gutman, A. B., and Yu, T. F.: Am. J. Med. 13:744, 1952. (10) Kusell, W. C.: Annual Review of Medicine, Stanford, Annual Reviews, 2:267, 1951. (11) Kusell, W. C., and Schaffarick, R. W.: Bull. on Rheu-

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REFERENCE: 1. New York State J. Med. 50:2293, 1950.

ANNALS OF INTERNAL MEDICINE

VOLUME 40

JANUARY, 1954

NUMBER 1

PROBLEMS IN CARDIOVASCULAR SURGERY *

By JAMES V. MALONEY, JR., M.D., and ALFRED BLALOCK, M.D.,
Baltimore, Maryland

UNTIL relatively recently surgery of the heart and great vessels was limited largely to the suturing of wounds, the drainage of infections, the removal of scar tissue surrounding the heart, and the wiring of aneurysms. Although the treatment of the vast majority of patients with heart disease continues to be nonoperative in nature, there has been a great increase in the volume of cardiovascular surgery in the past decade. The advances are due to the joint efforts of surgeons, cardiologists and physiologists.

The surgical therapeutic advances have emphasized the necessity for more accurate diagnosis and for a better understanding of disease processes. For example, it is no longer adequate to state simply that the patient has congenital heart disease or acquired heart disease; the type of deformity must be determined. Whereas advances in diagnosis have increased the scope of surgery, so have the findings at operation added knowledge which increases the accuracy of diagnosis. Much may be learned at the time of operation by palpation of the exterior of the heart and great vessels and even more, in some instances, by inserting a finger into the interior of the heart. For example, digital exploration of the mitral valve through the left auricular appendage has emphasized the difficulties in differentiating by auscultation between mitral stenosis and insufficiency, and has caused some cardiologists to alter their interpretation of heart sounds. The important point is that knowledge has been extended rapidly by the combined efforts of physicians and surgeons. Until recently the physician has probably been too reticent to recommend operation for patients with an otherwise hopeless mechanical type of heart disease. An example in point is the experience of Souttar¹ who, in 1925, digitally dilated a stenotic mitral valve

* From the Symposium on Cardiac Surgery presented at the Thirty-Fourth Annual Session of the American College of Physicians, Atlantic City, New Jersey, April 17, 1953.
From the Department of Surgery of The Johns Hopkins University and Hospital.

through the auricular appendage and the patient was improved. Despite this success, he was not referred other suitable patients by his medical colleagues. On the other extreme, the surgeon of today in his enthusiasm may be too apt to recommend operation. Some of the surgical procedures are so new that there has not been time for evaluation. The fact that a patient survives does not indicate that operation was justified. The patient himself, in his enthusiasm and desire to get well, may be swayed in his evaluation of operative results.

These remarks lead us to return to the point that there should be close coöperation between the physician and surgeon, for the patient as well as they will benefit by the association. The surgeon can certainly profit from the mature judgment of the physician. We make a plea that you do not regard your surgical colleague as a mere technician. As a result of his unique opportunity to correlate clinical findings with the actual mechanical dysfunction of the heart as determined by findings at operation, the surgeon has developed considerable skill in the evaluation of certain aspects of cardiovascular disease. It is probably unnecessary to state that the advice and help of the radiologist and anesthesiologist with their knowledge of heart disease are invaluable.

We have arbitrarily divided cardiovascular disorders into the following three groups from a surgical therapeutic viewpoint. It is obvious that some disorders are not included and, furthermore, that other surgeons could justifiably differ with us in the classification. Time will permit a brief consideration of only a few of the disorders. The classification is as follows:

- I. Disorders in the Treatment of Which Surgery May Accomplish Good or Excellent Results.
 - A. Acquired Lesions
 1. Constrictive Pericarditis
 2. Wounds of the Heart
 3. Systemic Arteriovenous Fistula
 4. Arterial Aneurysm
 5. Mitral Stenosis
 - B. Congenital Lesions
 6. Patent Ductus Arteriosus
 7. Coarctation of the Aorta
 8. Pulmonary Stenosis and Atresia
 9. Pulmonary Arteriovenous Fistula
 10. Anomalies of the Aortic Arch
- II. Disorders in the Treatment of Which Surgical Therapy May Result in Moderate Improvement.
 - A. Acquired Lesions
 11. Essential Hypertension
 12. Aortic Valvular Stenosis
 13. Intracardiac Tumors.

- B. Congenital Lesions
 - 14. Anomalies of Venous Return
 - 15. Transposition of the Aorta and Pulmonary Artery
 - 16. Auricular Septal Defects
- III. Disorders in the Treatment of Which Surgery Is of Doubtful Value or Suitable Methods Are Not Yet Fully Developed.
 - A. Acquired Lesions
 - 17. Coronary Arterial Disease
 - 18. Insufficiency of Heart Valves
 - B. Congenital Lesions
 - 19. Ventricular Septal Defects
 - 20. The Eisenmenger Complex
 - 21. Pulmonary Hypertension
 - 22. The Lutembacher Syndrome
 - 23. Anomalous Origin of Left Coronary Artery

ACQUIRED HEART DISEASE

A wound of the heart should be treated by the physician if a surgeon is not available. It is generally agreed that wounds of the heart should be operated upon if there is continuing bleeding to the outside or into the pleural cavity. There is some difference of opinion how the patient with uncomplicated acute tamponade without continuing bleeding should be treated. Under these circumstances, we are of the opinion that open operation should be deferred until the effect of at least one pericardial aspiration has been determined. It has been our experience that the majority of patients will respond favorably to one or more aspirations, that recurrent bleeding will not occur and that an open operation will not be necessary. However, an operating room team should be alerted in case an operation is necessary. It is interesting that the aspiration of only an ounce or two of blood may relieve the tamponade and permit the recovery of the patient without open operation.

Constrictive pericarditis is a well recognized clinical entity, often of indeterminate etiology, which usually presents few difficulties in diagnosis. It is likely that the tubercle bacillus is the most frequent etiologic agent. Positive points in diagnosis may include prominence of peripheral veins, elevated venous pressure, a quiet heart without murmurs, suppression of pulsations of the heart under the fluoroscope, ascites and pleural effusion.

The fundamental surgical problem remains the same as that enumerated by Delorme² many years ago, namely, the removal of the scar tissue which is constricting the heart and in some cases the great blood vessels. It is necessary to remove the scar overlying the epicardium as well as that which lines the pericardium. Recent clinical and experimental evidence indicates quite clearly that the most important part of the procedure is the decortication of both the right and left ventricles. It is usually unnecessary to decorticate the auricles. Our experience indicates that the best exposure is obtained

through the auricular appendage and the patient was improved. Despite this success, he was not referred other suitable patients by his medical colleagues. On the other extreme, the surgeon of today in his enthusiasm may be too apt to recommend operation. Some of the surgical procedures are so new that there has not been time for evaluation. The fact that a patient survives does not indicate that operation was justified. The patient himself, in his enthusiasm and desire to get well, may be swayed in his evaluation of operative results.

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 13. Intracardiac Tumors.

- B. Congenital Lesions
 - 14. Anomalies of Venous Return
 - 15. Transposition of the Aorta and Pulmonary Artery
 - 16. Auricular Septal Defects
- III. Disorders in the Treatment of Which Surgery Is of Doubtful Value or Suitable Methods Are Not Yet Fully Developed.
 - A. Acquired Lesions
 - 17. Coronary Arterial Disease
 - 18. Insufficiency of Heart Valves
 - B. Congenital Lesions
 - 19. Ventricular Septal Defects
 - 20. The Eisenmenger Complex
 - 21. Pulmonary Hypertension
 - 22. The Lutembacher Syndrome
 - 23. Anomalous Origin of Left Coronary Artery

ACQUIRED HEART DISEASE

A wound of the heart should be treated by the physician if a surgeon is not available. It is generally agreed that wounds of the heart should be operated upon if there is continuing bleeding to the outside or into the pleural cavity. There is some difference of opinion how the patient with uncomplicated acute tamponade without continuing bleeding should be treated. Under these circumstances, we are of the opinion that open operation should be deferred until the effect of at least one pericardial aspiration has been determined. It has been our experience that the majority of patients will respond favorably to one or more aspirations, that recurrent bleeding will not occur and that an open operation will not be necessary. However, an operating room team should be alerted in case an operation is necessary. It is interesting that the aspiration of only an ounce or two of blood may relieve the tamponade and permit the recovery of the patient without open operation.

Constrictive pericarditis is a well recognized clinical entity, often of indeterminate etiology, which usually presents few difficulties in diagnosis. It is likely that the tubercle bacillus is the most frequent etiologic agent. Positive points in diagnosis may include prominence of peripheral veins, elevated venous pressure, a quiet heart without murmurs, suppression of pulsations of the heart under the fluoroscope, ascites and pleural effusion.

The fundamental surgical problem remains the same as that enumerated by Delorme² many years ago, namely, the removal of the scar tissue which is constricting the heart and in some cases the great blood vessels. It is necessary to remove the scar overlying the epicardium as well as that which lines the pericardium. Recent clinical and experimental evidence indicates quite clearly that the most important part of the procedure is the decortication of both the right and left ventricles. It is usually unnecessary to decorticate the auricles. Our experience indicates that the best exposure is obtained

through a long left intercostal transpleural incision in the fourth interspace, the fourth and fifth costal cartilages being divided. Both the superior and the inferior vena cava may be exposed through this incision. It is particularly important to remove the diaphragmatic aspect of the pericardium from the heart, thereby allowing the heart greater freedom of motion in its systolic contraction.

Regarding the choice of time for decortication, it has been held previously that the active infection should have subsided, particularly if the tubercle bacillus was the offender. Antibiotic therapy may allow one to operate with safety during an earlier stage of the disease. No one has yet had sufficient experience with the combined use of surgery and antibiotic therapy to give an authoritative answer to this problem.

Aortic aneurysms present fascinating problems in therapy. They may be saccular or fusiform. The aneurysms of the thoracic aorta are usually saccular and are usually due to syphilis, although trauma may be the etiologic agent. Abdominal aneurysms are usually fusiform in shape and are due most often to arteriosclerosis. A variety of methods of therapy have been advocated. One of the best of these is that of Blakemore,² in which the aorta is constricted proximal to the aneurysm and fine heated wire is introduced into the sac.

Dramatic results have been obtained recently by Bahnson⁴ of Baltimore and by Cooley and De Bakey⁵ of Houston as a result of operations in which saccular aneurysms of the aorta are excised with closure of the neck of the sac and fusiform aneurysms are excised and replaced by an aortic homograft. Bahnson has excised successfully saccular aneurysms of the ascending aorta, of the arch, of the descending thoracic aorta and of the abdominal aorta. In addition, he has successfully replaced abdominal fusiform aneurysms by aortic homografts.

Results of the surgical relief of *mitral stenosis* are among the most pleasing which have been achieved in cardiovascular surgery. The operative procedure is straightforward, the symptomatic relief is usually pronounced and the operative mortality is low. If some means could be found for preventing embolism, the mortality would be well under 5 per cent.

The most difficult problem is the selection of the patient for operation. It is our belief that operation is indicated if the physical signs of mitral stenosis are accompanied by some of the symptoms of pulmonary engorgement such as dyspnea, cough, orthopnea and hemoptysis. Some surgeons who have had extensive experience in the treatment of mitral stenosis believe that the valvular lesion itself, whether symptomatic or not, is an indication for operation. The correct point of view will be determined only by close follow-up of the relatively asymptomatic patient with mild stenosis over a period of many years. Only then can it be determined if the stenotic lesion is progressive, if it seriously shortens life expectancy, and if hypertensive pulmonary vascular disease invariably results. If such is the case, then operation is indicated as soon as the diagnosis is made.

The coexistence of stenosis and insufficiency presents a challenging problem to the physician and surgeon, since, as we have indicated previously, present operative procedures for treating insufficiency are not fully satisfactory. A decision must be made as to whether stenosis or insufficiency is the predominant lesion. Pertinent questions include the following: Should operation be postponed until more satisfactory methods are evolved for treating insufficiency? Should operation be performed and mitral commissurotomy alone performed?—or should the additional hazard of treating the insufficiency be accepted? These problems are made more difficult by the fact that we have had to modify the dogmatic dependence which was once

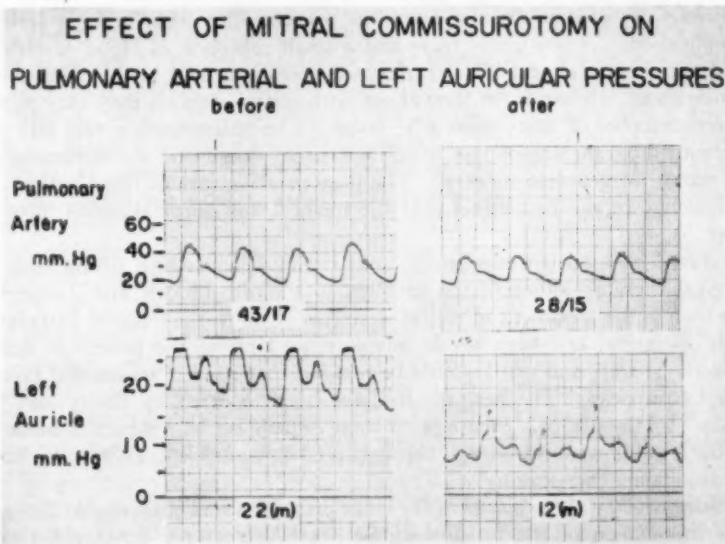


FIG. 1. These pressure tracings were made in the operating room several minutes before and several minutes after mitral commissurotomy. An immediate reduction in pulmonary vascular pressures resulted.

placed on auscultatory findings. Direct palpation of the functioning heart valve during life sometimes fails to confirm the impressions based upon murmurs located over specific areas of the chest wall.

Despite all of these difficulties in diagnosis, it is a tribute to our medical colleagues that the large majority of patients submitted to operation are greatly benefited, as indicated by symptomatic improvement and, to a lesser extent, as determined by pressure measurements. The tracings shown in figure 1, which were taken at the operating table immediately before and after mitral commissurotomy, show the marked reduction in left auricular pressure and pulmonary artery pressure that may result from the relief of

valvular stenosis. The pulmonary artery pressure decreased from 43/17 to 28/15 mm. of Hg, and the left auricular pressure from 22 to 12 mm. of Hg.

The need of medical and surgical teamwork is nowhere better illustrated than in the postoperative care of the patient who has had a mitral commissurotomy. Parenteral blood and fluid therapy must be adjusted to that rather precise amount which assures an adequate cardiac output without overloading the delicately balanced circulation. The activity of the patient in bed must be adequate to prevent hypostatic pneumonia and atelectasis, but must not be so vigorous that it places a burden on the recuperating cardiovascular system. Not infrequently the patient with a normal sinus rhythm will develop auricular fibrillation during the first postoperative week. The judicious use of digitalis and quinidine prevents this from being a serious complication. A low grade fever and a small collection of blood or pleural fluid accompany almost all intrathoracic operations and are usually of no significance. However, in the patient with mitral stenosis they may signal a recrudescence of acute rheumatic fever. The sedimentation rate and the electrocardiogram are of less than their usual diagnostic value because of the recent intracardiac surgery. The postoperative care of these patients is a challenge to the best effort that the medical and surgical teams have to offer.

Aortic stenosis is a mechanical constricting lesion which is amenable to surgical therapy, although the problem is a more difficult and dangerous one than is the treatment of mitral stenosis. Due to the dangers associated with operation, one hesitates to advise it as long as the patient is doing moderately well, and yet it should be realized that sudden myocardial failure is apt to appear. The best results have been reported by Bailey and his group⁶ by the use of a dilator with three expanding bars which is made to follow a guide wire introduced through the left ventricle. To say the least, the results are encouraging.

Insufficiency of the valves of the heart presents a real challenge in therapy. The mechanism of the functioning of heart valves is a complicated one. Even with the further perfection of the extracorporeal circulation, the treatment of insufficiency may remain a very difficult one. Bailey⁷ has abandoned the use of the pedicled transventricular pericardial graft after "further experiences with 48 human cases" in the treatment of mitral insufficiency. Probably the most encouraging results that have been obtained thus far in the treatment of mitral insufficiency are those by Harken, in which he anchors plastic material in the shape of a bottle in the mitral ring area; and those by Bailey, in which he sutures the lips of a part of the incompetent valves together with a strip of pericardium. Probably the most encouraging results in the treatment of aortic insufficiency are those of Hufnagel.⁸ He places a plastic valve in the descending thoracic aorta. The problem of valvular insufficiency is indeed a difficult one. Much additional experimental work is indicated.

CONGENITAL HEART DISEASE

Progress in the surgical treatment of congenital heart disease has been even more rapid than that in the acquired disorders. In general, the indications for surgery are more clear cut. A few remarks will be made about several of the types.

The isolated *patent ductus arteriosus* is to the surgeon one of the most pleasing of cardiovascular anomalies with which to deal. Obliteration of the systemic-to-pulmonary shunt leaves the patient with an essentially normal circulation. Operation is usually not performed until the child is two or more years of age. Ideally, operation should be performed in the first decade of life, before left ventricular hypertrophy and strain result from the excessive burden placed on the left ventricle by the systemic-to-pulmonary shunt. It is important to realize that a very large ductus may not be accompanied by the typical machinery murmur.

Coarctation of the aorta is best treated between the ages of six and 16 years. It is desirable to wait until the aorta has achieved most of its growth, when an anastomosis of maximal size can be expected. Operation should not be delayed beyond the twenty-first year if significant hypertension is present, even though the patient is symptom free. Symptoms may be delayed until the third, fourth and fifth decades, at which time arteriosclerosis and aneurysm formation make the operation formidable. However, age in itself is not necessarily a contraindication to operation, as illustrated by the fact that more than 40 per cent of our patients are over 21 years of age.

Similarly, if cardiac failure develops in infancy, we do not hesitate to resect the coarctation. Left ventricular enlargement in an infant of 10 weeks is shown in figure 2. With this x-ray plus clinical signs of left heart failure as the indications, this patient was operated upon with a successful outcome.

Stenosis of the pulmonary valve occurring as an isolated defect or with a patent foramen ovale may be satisfactorily treated by division and dilatation of the valve via the right ventricular route. It has been our custom to perform this operation if the child is symptomatic or has progressive cardiac enlargement, or if cardiac catheterization shows severe right ventricular hypertension. This policy is obviously not analogous to our policy of closing a patent ductus prior to the development of ventricular dysfunction. Therefore, we have more recently come to believe that the indications for surgery in this condition should be more liberal.

Pulmonary stenosis or atresia associated with a high ventricular defect and overriding of the aorta or, in other words, the *tetralogy of Fallot*, accounts for the largest portion of our experience in the surgery of congenital heart disease. Taussig and Bauersfeld,⁹ in reviewing the results of the first 857 patients with tetralogy of Fallot in whom a systemic-pulmonary artery shunt was created, found that 78 per cent had a good result from operation.

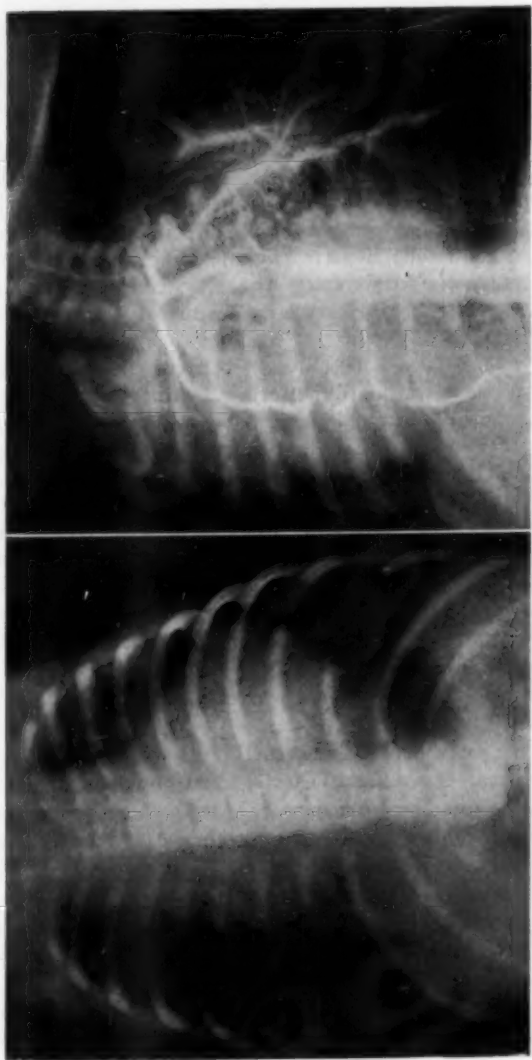


FIG. 2. Roentgenogram on the left shows marked cardiac enlargement in an infant of 10 weeks. Aortogram on right demonstrates a coarctation of the aorta.

The operative mortality was 15 per cent, a figure which is not high when considered in the light of the poor prognosis without surgery.

The surgical treatment of *transposition* of the great vessels, auricular and ventricular *septal defects*, and *anomalies* of the *venous return* is in the developmental stage. Clinical and experimental results in the treatment of some of these conditions have been excellent in some cases. It is apparent, however, that further investigative effort is required before these operations can approach the results that have been achieved in the therapy of congenital and acquired valvular stenosis.

The *diagnostic examination* of the usual case of congenital heart disease requires radiographic and fluoroscopic studies, together with a clinical examination by a physician experienced in dealing with cardiac anomalies. Cardiac catheterization, angiocardiology and aortography are reserved for cases in which the diagnosis is in doubt. The physiologist, with his specialized knowledge of circulatory dynamics, may be particularly helpful in the study of such cases. The severe degree of polycythemia which is often associated with cyanotic heart disease is prone to cause cerebral thrombosis. Hemoconcentration should therefore be avoided during the preoperative and postoperative periods and during acute febrile illnesses by maintaining adequate fluid intake. The cyanotic child must be hydrated to the precise degree which will prevent vascular thrombosis, but which will not overload the failing circulation.

Digitalis is not ordinarily used in the preoperative preparation of these patients with congenital heart disease except in the presence of overt myocardial failure. Because of the susceptibility of such patients to bacterial endocarditis, *antibiotics* are begun on the day preceding operation and continued for one week, or until the patient is afebrile. Despite the existence of multiple potential avenues of infection at the time of surgery, our incidence of bacterial endocarditis following operations for the tetralogy of Fallot has been remarkably low—about 2 per cent. Most cases respond favorably to penicillin therapy. It is particularly important to give antibiotics to patients with coarctation of the aorta because infection at the suture line is usually a fatal complication.

CONCLUSIONS

From this cursory review it is apparent that cardiovascular surgery calls for a close integration of the efforts of the physician and the surgeon. In this particular group of patients the use of digitalis and diuretics, the problems in fluid therapy, the treatment of cardiac arrhythmias, the therapy of endocarditis and other mutual problems transcend what were once considered the boundaries between the medical and surgical specialties. At a time when a number of the various interests in medicine are growing farther apart as the natural result of their increasing complexity, it is refreshing to note the development of a field which reunites the efforts of the physician and surgeon.

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PYLORIC OBSTRUCTION IN PEPTIC ULCER*

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INTRODUCTION

ONE of the important complications of peptic ulcer is gastric retention. This is usually due to narrowing, which in some cases is in the duodenum instead of at the pylorus. In either case, however, it is generally referred to as pyloric obstruction. The narrowing may be caused by spasm and edema secondary to an active ulcer, scar tissue formed in the healing of an ulcer, or a combination of both of these factors. It is important to determine the major cause of this obstruction, for whereas an active ulcer with spasm and edema might respond to medical treatment, scar tissue would require surgery. Some differences in history and laboratory and roentgenologic findings of the two types of obstruction have been pointed out, but they have not been considered diagnostic, and most authors indicate that medical therapy should be tried in every case. There is, however, a difference of opinion as to how long medical therapy should be tried; some authors state that three days^{1,2} is sufficient, others suggest five to 10 days,^{3,4,5} and some even recommend several weeks.^{6,7,8} There is also some question as to the ultimate fate of the cases that initially respond to medical management. There is evidence that a large proportion of them have a recurrence of their gastric retention and finally require operation.⁸

We studied the records and conducted a follow-up examination of the cases of peptic ulcer with gastric retention seen at the Cleveland Veterans Administration Hospital between July, 1946, and October, 1951, to determine the differences in history, laboratory, and roentgenologic findings between patients with gastric retention due to an active ulcer and those with retention due to scarring, the length of time that medical therapy had to be continued in the cases in which it was successful, and the status at follow-up of patients who responded to medical management during their first hospitalization.

METHODS OF STUDY

Eighty-seven cases of peptic ulcer with gastric retention seen consecutively in this hospital between July, 1946, and October, 1951, were studied. Those patients with peptic ulcer were considered to have gastric retention who had either retention of barium at six hours or, on morning aspiration, had over 100 c.c. of fluid or retained food in the stomach.

All patients were given a trial of medical therapy. This varied somewhat, as they were treated by different physicians, but it was generally as

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follows: A stomach tube was passed and then connected to a Wangenstein suction apparatus. The stomach was emptied. Feedings of 100 c.c. of malted milk containing added lactose, or of a milk-and-cream mixture, were then given every hour on the hour. Atropine, antacids, sedatives and sufficient parenteral fluids to maintain hydration and electrolyte balance were also given. The stomach was aspirated by the Wangenstein suction for 15 minutes at the end of every two hours, and the volume and character of the material aspirated were recorded. The patients were usually kept on this régime for about four days, but the period varied with their response to therapy. After the stomach tube was removed, aspirations were performed twice a day, in the morning and in the evening, either at bedtime or six hours after the last meal. If large amounts of food or fluid were obtained from these aspirations, patients were returned to the intermittent suction régime; otherwise, they continued to have aspirations once or twice daily until less than 100 c.c. of aspirate was obtained in the morning. Then, as their diet was liberalized, they were aspirated intermittently to determine whether retention recurred. If retention did not clear up, or if it recurred, operation was performed.

Patients who responded to medical therapy alone, and hence were not operated upon during their initial hospitalization, have been divided into two groups for purposes of study: those who had a later recurrence of their gastric retention, and those who did not. To determine whether there was a recurrence, special follow-up examinations on all medically treated patients were conducted between July and October, 1951. These examinations were from three to 65 months after the original medical treatment, the median follow-up being 26 months and the average time of follow-up being 27 months. Four patients who could not be followed were dropped from the study.

Fifty patients ultimately were operated upon, 39 during their first hospitalization and 11 during a later hospitalization. These 50 patients were divided for purposes of comparison into those showing significant narrowing and those showing slight or no narrowing of the pylorus or first portion of the duodenum at operation. Patients were considered to have significant narrowing of this pyloroduodenal region when the diameter of the lumen was reduced to less than 1 cm., or the operator could not introduce his little finger through it. The group with significant narrowing was further subdivided into cases with marked and moderate narrowing, those with the diameter of the opening between 0.5 and 1.0 cm. being considered moderately narrowed, and those with the diameter below 0.5 cm., markedly narrowed, in accordance with the criteria outlined by Palmer.⁹

In this and other studies, the narrowing that caused gastric retention was frequently found in the duodenum rather than at the pylorus. We have therefore considered the term "pyloroduodenal obstruction" more descriptive than the usual term "pyloric obstruction," and have used it in this report.

All patients had initial gastrointestinal x-ray studies with six hour films for evidence of retention. These were repeated after two and after four weeks of therapy in most cases. Blood chlorides, CO_2 combining power, blood urea nitrogen and nonprotein nitrogen were determined every three days while the patients were on intermittent suction.

The clinical and laboratory findings of 50 patients with peptic ulcer without evidence of pyloric obstruction were also analyzed, for comparison with the obstructed group.

OBSERVATIONS

Gastric retention was not suspected from the clinical history in all of the 87 patients who showed it on x-ray and gastric aspiration. It was, however, suspected from history alone in most of the 38 patients who had definite pyloroduodenal obstruction later demonstrated at operation. There were a number of differences between the histories of these 38 patients (column 2, tables 1 and 2), and the histories of 50 peptic ulcer patients without evidence of obstruction (column 1, tables 1 and 2). The patients with obstruction were older, the majority being over 40, whereas those without evidence of obstruction were generally under 40. The obstructed patients tended to have a longer history of ulcer, usually over five years and often over 10. They had complications more frequently, almost a third having had a previous hemorrhage, and more than a third having had a previous perforation. In contrast, only a fifth of those without obstruction had had previous hemorrhage, and only one in nine a previous perforation. The obstructed patients that had pain were less frequently relieved by antacids and food than were those who were not obstructed. In fact, their pain was often aggravated by eating, or they developed bloating or discomfort. The vast majority of them were relieved of their pain by vomiting.

Most of the nonobstructed patients gave a history of vomiting, and three of the obstructed patients did not. The obstructed patients who did vomit, however, gave a history of having vomited for much longer periods than those without obstruction. Patients with obstruction had often vomited for over six months, whereas most of the patients without obstruction had vomited for less than a month before admission. The obstructed patients also vomited more regularly, most of them one or more times a day, whereas most unobstructed patients vomited at irregular intervals. Yet it was not uncommon for a markedly obstructed patient, particularly after being obstructed for weeks, to vomit only once a day, while an occasional unobstructed patient had vomited after every meal. The obstructed patients frequently vomited large quantities, over a pint or even over a quart at a time. Their vomitus characteristically contained retained material and vegetables such as carrots and spinach, eaten hours before, could be recognized in the vomitus. In addition, the obstructed patients lost more weight; those without obstruction usually lost some weight with their attacks, but generally less than 10 pounds.

TABLE I
Clinical Histories of Peptic Ulcer Patients with and without Gastric Retention

	Patients without Retention	Patients with Gastric Retention			
		Patients Surgically Treated		Patients Medically Treated	
		Significant Pyloro-duodenal Narrowing	Slight or No Pyloro-duodenal Narrowing	Without Later Recurrence	With Later Recurrence
Total No. of Cases	50	38	7	28	16
Ages: 20-40	38	14	2	17	6
Over 40	12	24	5	11	10
Duration of Ulcer Symptoms					
0-1 year	9	2	1	2	0
1-5 years	15	8	2	14	5
5-10 years	21	14	0	5	6
Over 10 years	5	14	4	7	5
Total No. of Previous Hospitalization for Ulcer:					
None	25	3	1	13	1
1	16	12	2	8	9
2	5	10	0	2	4
3	1	8	1	4	1
4 or more	3	5	3	1	1
Previous Hospitalization for Obstruction	0	14	1	0	0
Previous Hemorrhage	9	11	2	2	4
Previous Perforation	5	13	1	4	4
Characteristics of Pain:					
Relieved by Antacid	34	20	3	16	11
Not Relieved	8	11	2	6	5
Not Determined	8	7	2	6	0
Relieved by Milk and Other Foods	39	9	4	20	6
Not Relieved	9	23	2	4	7
Not Determined	1	6	1	1	1
Relieved by Vomiting	11	22	5	4	13
Not Relieved	19	4	0	3	0
No Vomiting or Relief Not Determined	20	12	2	13	3
Weight Loss:					
None	11	3	0	8	3
Less than 10 Pounds	14	2	0	3	2
More than 10 Pounds	6	21	5	7	7
Not Determined	19	12	2	10	4

When the patient's history presented the characteristic features just discussed, the diagnosis of pyloric obstruction was easily made, but many of the 87 patients, including even some of the 38 patients with subsequently proved obstruction, did not present a typical history. In these cases, pyloric ob-

struction was recognized only after gastrointestinal x-ray studies and gastric aspiration for retention.

Of the 87 patients, 48 (or 55 per cent) responded to medical treatment during their first hospital admission. Follow-up studies were obtained on 44 of them. Twenty-eight had had no further evidence of pyloroduodenal obstruction. The remaining 16 had had a recurrence of their obstruction which either had brought them to a hospital before follow-up or was demonstrated during the follow-up study. In two patients there had not been

TABLE II
Characteristics of Vomiting in Peptic Ulcer Patients with and without Gastric Retention

	Patients without Retention	Patients with Gastric Retention			
		Patients Surgically Treated		Patients Medically Treated	
		Significant Pyloro-duodenal Narrowing	Slight or No Pyloro-duodenal Narrowing	Without Later Recurrence	With Later Recurrence
Vomiting:					
Present with this attack	32	35	7	10	15
Not present	18	3	0	9	1
Duration:					
Less than 1 week	10	2	1	4	0
1 week-1 month	7	7	0	5	4
1 month to 6 months	8	8	1	1	5
Over 6 months	7	18	5	1	6
Frequency:					
Less than once a day	27	7	4	13	9
1-3 X a day	3	20	1	2	5
Over 3 X a day	0	8	2	3	0
Greatest amount vomited at one time:					
Less than 500 c.c.	26	8	1	1	3
More than 500 c.c.	0	15	2	1	9
Not determined	6	12	4	17	3
Retained material vomited	2	21	3	3	11
Not vomited	24	2	1	4	0
Not determined	6	12	3	12	4

symptoms of obstruction, although we found 90 per cent gastric retention of barium at six hours in one and 40 per cent in the second. In the other 14 patients, symptoms of retention had recurred in from 10 days to 48 months, the median period being three months after their last hospitalization. Fourteen out of the total group of 16 eventually had operation performed for obstruction (11 at this hospital).

If one compares the clinical histories of the 16 medically treated patients who relapsed with those of the 28 medically treated patients who did not relapse (columns 4 and 5, tables 1 and 2), one notes definite differences.

These are similar to those just described, for the clinical histories of the patients who did relapse were like those of the 38 patients with proved obstruction, whereas the histories of the patients who did not relapse were similar to those of the 50 peptic ulcer patients without obstruction.

Laboratory evidence of obstruction tended to be slight in the 28 patients who did not have relapses after medical treatment. Nine of them had no retention of barium at six hours, and only seven (or one-quarter of them) had over 25 per cent retention of barium at six hours in their initial gastrointestinal x-ray series (column 3, table 3). In contrast, nine (or over one-half), of the 16 patients who relapsed had over 25 per cent retention of barium at six hours (column 4, table 3). In addition, smaller amounts of material were generally obtained on gastric aspiration from the patients who did

TABLE III
Initial Laboratory Evidence of Gastric Retention

	Patients Surgically Treated		Patients Medically Treated	
	Significant Narrowing	Slight or No Narrowing	Without Recurrence	With Recurrence
Fasting Morning Aspiration:				
Less than 100 c.c.	7	0	8	1
100-200 c.c.	5	4	7	5
200-400 c.c.	6	1	5	2
Over 400 c.c.	5	0	0	2
Evening Aspiration:				
Less than 100 c.c.	1	0	1	0
100-200 c.c.	2	1	1	2
200-400 c.c.	2	1	2	5
Over 400 c.c.	16	3	3	4
Six Hour Barium Retention:				
None	7	0	9	1
Less than 25%	7	0	12	4
25-50%	7	2	6	7
50-75%	5	4	1	1
75-100%	11	1	0	1

not relapse. Only five of 20 patients aspirated in this group (or 25 per cent) had over 200 c.c. on a morning aspiration, whereas four of 10 patients who did relapse (or 40 per cent) had over 200 c.c. retention on a morning aspiration. Evening aspirations were performed on all groups but were not consistently done six hours after eating, and were therefore not considered so significant as the morning aspirations unless large amounts of material were aspirated.

At the end of one week only two of the 28 patients who did not relapse still required aspiration, whereas 12 of the 16 who did relapse still required aspiration at the end of one week, and several showed retention at the end of three weeks of treatment.

It is therefore evident that the patients who were to have a future recur-

rence of obstruction had more gastric retention by x-ray and aspiration than those who did not. Furthermore, the patients with a later recurrence of their obstruction failed to respond to treatment as rapidly as did the others.

A total of 50 patients were operated upon for their obstruction, 39 during their initial hospitalization and 11 after a relapse. Thirty-eight of the total group (or 76 per cent) were found at operation to have significant narrowing of the pylorus or duodenum; seven (or 14 per cent) were found to have slight or no narrowing, and in five (or 10 per cent) the degree of narrowing was not accurately determined (table 5). Two of the seven with no actual narrowing did have angulation of the pyloroduodenal region secondary to

TABLE IV
Clinical History and Laboratory Findings in Patients with Marked and Moderate Narrowing of the Pyloroduodenal Region

	Marked Narrowing: Diameter of Narrowed Area Less than 0.5 cm.	Moderate Narrowing: Diameter of Narrowed Area from 0.5-1 cm.
Duration of Ulcer Symptoms:		
Less than 5 years	7	3
Over 5 years	3	25
No. of Hospitalizations for Ulcers:		
None	3	0
1	3	9
2	3	7
3 or more	1	12
Duration of Vomiting:		
Less than 6 months	3	12
Over 6 months	7	11
No vomiting	0	3
Six Hour Barium Retention on Admission:		
None	1	6
Less than 25%	1	6
25-50%	2	5
50-75%	1	4
Over 75%	5	6
Total Number of Cases	10	28

adhesions to neighboring organs, which might have been responsible for their obstruction.

As the number of patients without significant narrowing was small, it was not possible to draw conclusions of statistical value in comparing them to the group significantly narrowed at operation. However, a few differences are worthy of mention. The patients without significant narrowing had fewer complications (column 3, tables 1 and 2). Only one out of seven had had a previous perforation, whereas 13 of the 38 patients with significant obstruction gave a history of previous perforations. Those without significant obstruction were usually relieved of their pain by food, whereas those with actual obstruction were not. Those without significant obstruction vomited less often and frequently gained weight during treatment.

In 10 of the 38 patients with significant obstruction, there was such marked narrowing of the pylorus or duodenum that a Kelly clamp either could be barely passed through the narrowed area or could not be passed at all. There were a few differences between this group and the group of obstructed patients as a whole (table 4). Seven of the 10 patients gave a history of ulcer symptoms for less than five years, whereas 25 of the 28 who had less marked narrowing had had ulcer symptoms for over five years. The markedly obstructed patients had had fewer hospitalizations for ulcer: three had had none, and only one had had more than two. All of the moderately obstructed patients had had at least one hospitalization, and 12 had had three or more. The 10 markedly obstructed patients all had a history of vomiting, seven of them for over six months. In contrast, less than half of the moderately obstructed group had vomited for over six months, and three had never vomited at all. Large volumes were aspirated in the morning and evening from both groups, but five (or half) of the markedly obstructed group had over 75 per cent barium retention at six hours, whereas only six of the 28 moderately obstructed cases had this much retention. There were no striking differences in the response to treatment between the two groups.

Thus, the markedly obstructed group had not recognized symptoms of ulcer or sought hospital care as often as the moderately obstructed patients. They had usually vomited for over six months prior to hospitalization and had had marked barium retention prior to treatment.

At operation it was found that almost half of the patients had active ulcers (table 5). The sites of obstruction were approximately equally divided between the pylorus and the first portion of the duodenum. It was difficult in some cases, however, to determine the exact site and degree of obstruction as well as the activity of the ulcer. This was particularly true in those cases in which vagotomy and gastroenterostomy rather than gastrectomy were performed.

Six patients were found to have evidence of gastric ulcers, and in only one of these was the ulcer healed. One of the patients had a gastric ulcer above the angulus, but in all other cases, the ulcer was below the angulus. Twenty-eight patients had duodenal ulcers, half of which appeared to be healed. Five duodenal ulcers showed penetration into the pancreas. In 16, there were adhesions to neighboring organs, interpreted by the surgeons as consistent with perforation. Several of these patients did not give a history of an acute perforation which had been recognized in the past.

The proportion of active ulcers found at operation in the group with slight or no narrowing was higher than in the other groups. Six of the eight patients in this group had active ulcers.

The stomach was found to be dilated in 19 and its wall hypertrophied in 17 of the patients operated upon. All but one of these patients were in the significantly narrowed group. In this last patient the degree of narrowing had not been determined.

An analysis of the free and total acid concentration of the gastric juice in the fasting state and following histamine or insulin stimulation failed to reveal any significant differences between the obstructed patients who at operation had marked, slight or no narrowing. When the obstructed ulcer patients as a whole were compared to the group of 33 nonobstructed ulcer patients, it was found that nine (or 27 per cent) of the nonobstructed group had no free hydrochloric acid in the fasting specimen, whereas all of the obstructed group had free acid present initially. The rise in free acid fol-

TABLE V
Findings at Operation in 50 Patients with Gastric Retention

	Marked Narrowing: Up to 0.5 cm. Diameter	Moderate Narrowing: 0.5-1 cm. Diameter	Slight or No Narrowing	Degree of Narrowing Undetermined
Total Patients	10	28	8	4
Active Ulcers: Total	4	12	6	2
Duodenal	2	10	4	1
Gastric	2	2	2	1
Healed Ulcers: Total	1	12	1	0
Duodenal	1	10	0	0
Gastric	0	2	1	0
Ulcers with Degree of Activity Undetermined-Duodenal	5	4	1	2
Ulcers Penetrating into Pancreas	1	5	0	0
Evidence of Previous Perforation of an Ulcer	4	11	0	1
Stomach Dilated	4	14	0	1
Stomach Hypertrophied	5	11	0	1
Narrowing at Pylorus	5	16	0	2
Narrowing of Duodenum	5	12	2	2

lowing histamine stimulation was almost the same in both groups (table 6), the obstructed patients showing only slightly higher values.

DISCUSSION

Pyloric obstruction is considered a common complication of peptic ulcer, but, as Palmer¹⁰ has pointed out, the term "pyloric obstruction" has been loosely used. It has been applied to any case of peptic ulcer with gastric retention. This retention may actually be due to hypomotility of the stomach, spasm of the pylorus or duodenum, or obstruction of the lumen of the pylorus or duodenum by edema, as well as to narrowing of this lumen by scar tissue. Narrowing of the pylorus or duodenum by scar tissue alone

is frequently demonstrated in cases of peptic ulcer at autopsy. In one series¹¹ it was found to be present in 4.3 per cent of 1,269 cases. In another study,¹² 23 per cent of 230 cases of duodenal ulcer and 5.8 per cent of 173 cases of gastric ulcer had cicatricial obstruction. In a third investigation,¹³ 7.5 per cent of 120 patients whose essential lesion at autopsy was peptic ulcer were reported to have stenosis.

The clinical incidence of pyloric obstruction reported by different authors also varies somewhat, but it tends to be higher than the autopsy incidence, probably because clinically the term is usually applied to any peptic ulcer patient showing significant gastric retention, whether this is due to scarring or other cause. Wilkinson¹⁴ stated that pyloric obstruction occurs in approximately one tenth of all ulcer cases. Emery and Monroe¹⁵ found evidence of obstruction in 11.7 per cent of 1,435 cases of peptic ulcer. They emphasize the point that in their group they did not include cases showing

TABLE VI

Free Hydrochloric Acid Concentration in Obstructed and Nonobstructed Ulcer Patients in the Fasting State and Following Histamine Stimulation

Clinical Units Free HCl	Cases Significantly Obstructed		Cases not Obstructed	
	Fasting	After Histamine	Fasting	After Histamine
0	0	0	9	1
0-20	4	0	5	0
20-40	14	0	12	1
40-60	6	6	6	12
60-80	6	12	1	15
80-100	0	2	0	3
100-120	0	7	0	1
Total Cases Tested	30	27	33	33

gastric retention due to some cause other than obstruction of the pylorus or duodenum. Berkman¹⁶ found evidence of obstruction in 22 per cent of 97 gastric ulcers and in 16 per cent of 582 duodenal ulcers. He used the clinical picture, gastric aspirations and the six hour retention of barium as guides. Brown⁶ stated that pyloric obstruction could be considered the most common complication of peptic ulcer. Of 1,224 cases of peptic ulcer studied, he noted that 34 per cent complained of being awakened from sleep with pain which, he felt, was usually caused by delayed emptying due to pyloric obstruction. Thus it can be seen that the incidence reported varies with the criteria used by different authors.

Our criteria for gastric retention as evidence of pyloric obstruction consisted of the presence of over 100 c.c. of fluid in a fasting morning aspiration, or the retention of barium in the stomach six hours after its administration. In accordance with these criteria, 87 of the patients admitted to this hospital between July, 1946, and October, 1951, were found to have gastric retention. It was at times difficult to determine the presence or absence of pyloro-

duodenal obstruction in these patients from their symptoms alone. The mere presence of vomiting, often felt to be indicative of pyloric obstruction, was misleading, for it occurred frequently in ulcer patients without obstruction. However, when vomiting was productive of large amounts of material and contained food eaten several hours previously, it became an important diagnostic clue. On the other hand, in the absence of significant vomiting, when a patient had pain which did not respond to the usual medical regimen, he was at times found to have pyloroduodenal obstruction.¹⁷

We found neither x-ray examination nor gastric aspiration for retention completely reliable in determining whether obstruction was present in those cases where the clinical picture suggested it. Thus, several patients proved at operation to have obstruction showed no retention of barium by x-ray at six hours. Similarly, several patients proved at operation to have obstruction did not show retention on aspiration of the fasting stomach contents. This corresponds to the experience of Berkman,¹⁶ who reported 85 cases in whom appreciable narrowing of the pylorus was demonstrated at operation but in whom no clinical or laboratory findings of retention were noted. Bockus¹⁸ also found discrepancies between clinical evidence of retention and retention of barium at six hours by x-ray, for, of 77 cases who had retention by aspiration and were studied by x-ray, only 43 per cent had barium retention at six hours.

Once it was decided that a patient showed evidence of pyloric obstruction, we adopted the procedure usually advocated, of placing the patient on a medical regimen of frequent bland feedings and aspirations to relieve gastric retention.

Forty-four (or slightly more than half) of our 84 patients responded to this medical regimen during their first hospitalization for obstruction. This is less than the percentage reported by several authors. Palmer¹⁰ stated that, in keeping with Sippy's earlier comments, about 85 per cent of obstructed patients would respond initially to medical management. Seley³ reported that 62 of his 72 obstructed patients were managed medically, and 70 of the 79 cases studied by Jordan and Kiefer¹⁷ were likewise relieved by medical treatment. In contrast, Kress¹⁹ found that only 14 (or 41 per cent) of 34 patients were relieved of their obstruction on a strict medical regimen.

It was not possible to predict in every case whether there would be a favorable response to medical management. We found, however, that there were certain elements in the history and initial laboratory findings that were usually associated with organic obstruction or scarring, and other features which tended to support a diagnosis of retention secondary to spasm and edema. In general, patients with organic obstruction were older, had a longer history of ulcer and had had more frequent hospitalizations. Their pain was often not relieved by antacids, was actually made worse by eating, but was relieved by vomiting. They had usually vomited for months, one or more times a day, and at times had vomited large amounts of material

containing retained food. They had frequently lost more than 10 pounds of weight with their illness. Many of them had had a history of a previous perforation or a history of previous treatment for obstruction.

Some of these points have been stressed by other authors. Berkman¹⁶ remarked on the frequency of a history of previous perforation. Collins and Rossmiller²⁰ stressed the importance of a history of previous treatment for obstruction. Lahey² emphasized the significance of the duration of a history of obstruction. Sixty-one per cent of his patients obstructed for less than three months were relieved by medical treatment, whereas only 31 per cent of his patients obstructed for over three months were similarly relieved.

Initial laboratory studies helped in the differentiation in that the patients without organic obstruction tended to have lesser degrees of gastric retention. Thus, they usually had less than 25 per cent barium retention on gastrointestinal x-ray series, and their morning aspiration usually amounted to less than 200 c.c. This tends to confirm the statement of Bockus that a six hour retention of barium of 25 per cent or less is usually not due to fibrosis.⁸ Nevertheless, this information was no more helpful in making a definite diagnosis than was the history. For example, seven patients had over 25 per cent barium retention by x-ray at six hours, yet responded well to medical treatment and had no recurrence through the period during which they were followed. Rafsky⁷ and Delario²¹ similarly reported patients with 24 and 48 hour barium retention who responded to medical management. Five of our cases who had retention of over 200 c.c. on their initial morning aspiration, and three who had over 400 c.c. on their initial evening aspiration, were permanently relieved by medical treatment.

Medical therapy in our cases was usually given for at least two weeks, and it was continued if the patient seemed to be improving and not losing weight. Other authors have suggested both shorter and longer periods of medical therapy: three days,^{1, 2} five to seven days,^{20, 22} seven to 10 days^{3, 23} and several weeks.^{6, 7, 8, 24} They have reported cases that responded only after many weeks, but then remained symptom-free during years of follow-up.⁸ We found that some patients responded to medical therapy after more than two weeks. However, all but two of our 28 patients who had no further recurrence of obstruction cleared in less than a week of medical therapy, whereas half of the 16 patients who had a subsequent recurrence of their obstruction required more than a week. Thus, it appeared that most of our patients who required over a week of treatment ultimately required operation.

The patient's clinical history was found useful in deciding whether to continue medical therapy in cases slow to respond. Patients who were relieved by medical therapy and had no later recurrence of retention had a history like that of the usual ulcer patient with no evidence of gastric retention. In contrast, the patients who had a recurrence had a history like that just described for patients with organic obstruction.

Where organic obstruction was demonstrated at operation, the site of narrowing was almost as often in the first portion of the duodenum as in the pylorus itself. This differed somewhat from the findings of Hurst and Stewart,¹² who noted that in about three quarters of their cases the obstruction was at the pylorus rather than in the duodenum. Severe narrowing of the lumen to the degree that a probe could just be passed through the area was seen in only 10 of our cases. In the other 28 with significant narrowing, the area involved would admit the tip of the little finger. Thus, narrowing, though present, was often not so marked as might have been suspected from the clinical picture.

Twelve of our 28 patients with moderate narrowing had active ulcers. This corresponds to some extent to the findings of Hurst and Stewart.¹² They noted that, of 17 patients showing stenosis of the duodenum, 10 showed an active ulcer. These observations suggested that the obstruction, in the duodenum at least, was often caused by a combination of moderate narrowing due to scarring and further narrowing due to edema and spasm secondary to an active ulcer. It would then seem that prolonged medical therapy should heal the active ulcer and hence would be advisable. Yet, of 18 patients in our group who received over four weeks of treatment and who were finally operated upon, 12 still had active ulcers at operation. It is apparent that the intensive ulcer treatment used in these cases failed to heal the ulcers. There are several possible explanations for this. Crohn²⁵ noted increased gastric acidity in patients with pyloroduodenal obstruction, which he attributed to the delayed emptying of the stomach. We also noted that free acid was present in fasting specimens in all of our pyloroduodenal obstruction cases, whereas this was not true in all of the cases of peptic ulcer without obstruction, and we found that the obstructed patients had, on the average, a slightly greater acidity after histamine administration than the nonobstructed ulcer patients. Another possible explanation for the fact that many of these ulcers healed slowly is that they were often of the callous type, as noted by Held and Goldbloom²⁶ and Crohn²⁵ in their series. Further, in our group of cases the ulcer often showed evidence of penetration into neighboring organs, or adhesions about the ulcer indicated a localized perforation. The poor nutritional status of these patients may have been still another factor in the failure of these ulcers to heal with adequate medical treatment. A question that remained was whether a medical regimen different from the one we utilized might have been more successful in curing the ulcers in these cases.

SUMMARY

The data on 83 patients with peptic ulcer and gastric retention are reviewed. All were given a trial of medical therapy. Forty-four responded initially, but, at or before follow-up, gastric retention had recurred in 16. The retention had usually cleared within a week of institution of medical therapy in the patients who did not have a recurrence, whereas a longer

period had often been required in those that later had a recurrence. The patient's clinical history and laboratory findings often indicated whether he was likely to be relieved by medical therapy. The patients that came to surgery on their first or subsequent admissions and had organic obstruction, characteristically were older, had a longer history of ulcer, had more complications, had vomited for a longer time and more regularly, had vomited larger quantities, and had often brought up retained food. Their laboratory evidence, retention of barium by x-ray and gastric residue on aspiration were also usually greater.

Fifty patients were operated upon for persistence or recurrence of their gastric retention. Thirty-eight were found to have definite narrowing in either the duodenum or the pylorus. Active ulcers were present in almost half of the cases in spite of the previous medical therapy. Obstruction often appeared to be due to the effect of an active ulcer in a duodenum or pylorus already narrowed by previous scarring.

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EFFECT OF ORAL POLYMYXIN B ON *PSEUDOMONAS AERUGINOSA* IN THE GASTRO-INTESTINAL TRACT *

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IN 1882 Gessard¹ identified the microorganism *Pseudomonas aeruginosa* (*Bacillus pyocyaneus*) and described some of its characteristics. Seven years later Charrin² demonstrated the pathogenicity of several strains in animals. Since then there have been numerous publications concerning this bacterium. In 1906 Fraenkel³ reported 26 fatal cases of pseudomonas infection, 21 in children under two years of age. In six the gastrointestinal tract was involved. Cooley⁴ reported an outbreak of diarrhea which affected 37 children in an institution and which resulted in nine deaths. Escherich⁵ reported four fatal cases of infantile diarrhea due to this organism. Baginsky⁶ reported two cases, one of which died. The latter had positive blood and stool cultures. Lartigan⁷ reported an outbreak involving six children which was traced to contaminated well water. There were three deaths. Wollstein⁸ described infants with ulcerative gastritis due to this organism. Dudden⁹ found pseudomonas in the stomach and later in an abscess of the liver in a case of infantile diarrhea. Waite¹⁰ and Wassermann¹¹ reported fatal cases in children who developed liver abscesses apparently secondary to their intestinal infections.

Schaffer and Oppenheimer¹² reviewed the pathologic characteristics of *P. aeruginosa* infections in infants and children and demonstrated in a series of cases that this organism can cause serious and often fatal infections. The pathogenicity of this organism, especially for infants and children, has been studied more recently by Kagan and coworkers¹³ and by Walker.¹⁴ From the various studies cited it has become clear that this organism can invade the body from the intestinal tract under circumstances which are not well understood, and that the infections are serious and are often fatal.

Epidemics of diarrhea in newborn nurseries have been traced to the spread of *P. aeruginosa*.^{12, 15, 16} These studies led to the present one, the purpose of which was to determine the effect of the new antibiotic, polymyxin B (Aerosporin), on the organism in a carrier, and also on acute infections possibly due to this organism, with a view to therapy in adults who may transmit it to others. This may be especially important in personnel from whom transmission to newborn infants may be feared.

In September, 1947, there appeared in *The Lancet*¹⁷ a short note concerning a newly isolated antibiotic which has since been referred to as poly-

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myxin A. It appeared that this antibiotic, a product of the *Bacillus aerosporus* isolated from the soil of a Surrey garden, was selectively bactericidal to certain gram-negative bacteria. It is a basic polypeptide plus a fatty acid component. Different antibiotics of similar nature have been isolated from various strains of *B. aerosporus*, and they have been called polymyxins B, C, D and E. The polymyxins differ from each other in amino acid composition and speed in partition chromatography. Much of the earlier clinical work was done with polymyxin D, and it was reported to cause renal damage.¹⁸ Polymyxin B, however, was found to be relatively free of nephrotoxicity.¹⁹

Finland and coworkers,¹⁹ by in vitro studies, found polymyxin B (Aerosporin) most effective and polymyxin D next most effective against 267 strains of *P. aeruginosa*. They also showed that streptomycin was active against a majority of strains only in very high concentrations, and that Aureomycin and chloramphenicol (Chloromycetin) were inhibitory only in concentrations outside the accepted clinical range. Kagan and co-workers,¹³ in 1951, showed that polymyxin B was a most effective drug against this organism both by in vitro tests and by clinical experience, and that it is relatively free of renal toxicity. This was confirmed by Jawetz.²⁰

METHOD

Stools were obtained from all nursing personnel assigned to work in the newborn nursery and in the children's hospital (Sarah Morris Hospital), and also from all female personnel during the preemployment examination, and all female personnel with gastrointestinal symptoms. The nurses were graduates or students of Michael Reese Hospital and affiliating institutions. Stools were submitted promptly after passage, and the bacteriologic cultures were started shortly thereafter. Routine bacteriologic procedures were utilized.

When *P. aeruginosa* was found, 150 mg. of polymyxin B* were given orally every eight hours for seven days. Only those individuals awaiting assignment to the newborn nursery or the children's hospital were given the drug. All those who were not expected to work with infants or children served as controls.

On the fifth day of treatment the subjects returned for questioning regarding the appearance of new symptoms or side effects due to the drug, and each submitted a stool that day or within 24 hours. Additional stool examinations were done on the twenty-fifth and thirtieth days after the start of therapy.

RESULTS

Of 273 female personnel examined, 32 had stool cultures positive for *P. aeruginosa*. (This frequency cannot be interpreted as an index of usual

* Tablets of polymyxin B (Aerosporin) containing 50 mg. each were used.

prevalence in this area, since epidemiologic studies suggested a potential source of the organism for this group of individuals.) Twenty-four were treated and eight served as controls. In addition, a member of the male hospital staff and the daughter of another staff member were treated. Both of them had severe, acute gastrointestinal symptoms. *Pseudomonas* was the only organism found in their stool cultures which might have been responsible for their illness.

CONTROL CASES

The ages of the eight control cases ranged from 18 to 28 years (average, 22 years).

None had gastrointestinal symptoms. Three showed *P. aeruginosa* in the first stool cultures taken when they came to the hospital. In five, the cultures taken on their arrival were negative for pseudomonas, but several weeks later, when reexamined, they were found to harbor the organism. (A possible source for the latter five cases was found in a food handler whose stool cultures also revealed this organism in large numbers.)

One of the eight had received Terramycin three months previously because of exposure to psittacosis. At the time she received Terramycin she developed diarrhea which lasted five days.

On the follow-up stool examinations, three of the control cases had stool cultures negative for pseudomonas and five were still positive. This confirms previous impressions that a certain number of individuals who acquire or harbor this organism may spontaneously eliminate it. A thorough study of this phenomenon would be of interest. Spontaneous elimination of this organism within a four week period apparently may occur in almost half of such subjects.

TREATED CASES

The ages of the treated group of 24 cases ranged from 17 to 55 years (average, 22 years).

In 19 of the 24 cases there was a record of a previous stool culture negative for pseudomonas. The time interval between the preceding negative culture and the positive one varied considerably for the group, but with most it was three to eight weeks. One of the group had had *Cheilomastix mesnili* and a paracolon in her stool two months prior to the finding of the pseudomonas, and one had had *Endamoeba histolytica* two years before. In one case, *Dientamoeba fragilis* had been found in the initial stool examination nine months before *P. aeruginosa* was found.

Of the 24 cases in this group, nine had gastrointestinal symptoms for which there was no other demonstrable cause: one had abdominal cramps, one had recurrent episodes of diarrhea, three had acute diarrhea, and four complained of recurrent cramps and diarrhea. At the time *P. aeruginosa* was found, two had paracolon organisms in addition, one had *Proteus morganii* and one had *P. morganii* and *E. histolytica*.

All of the stool cultures were negative for pseudomonas after five days of treatment. However, at this time two still showed *P. morganii*, one still had paracolon, and three now harbored *P. mirabilis* which had not been previously found. The drug was given for two more days (a total of seven days) until 3,150 mg. in all had been taken.

In the follow-up stool cultures, pseudomonas was found in only one of 23* individuals in this group. This individual had given no history of gastrointestinal symptoms at any time and apparently was a carrier. At the time of the follow-up studies four showed *P. morganii*, two *P. mirabilis*, and one paracolon. One of the individuals with *P. morganii* also had *P. mirabilis*.

Of the two who were not part of the female personnel, the physician had cramps, diarrhea and malaise. He had *P. aeruginosa*, *P. mirabilis* and *P. morganii* in his initial stool culture. The pseudomonas was eliminated after the seven day course of polymyxin B, and the symptoms subsided in spite of the persistence of both *P. mirabilis* and *P. morganii*. Another patient, the daughter of a staff physician, was quite ill when *P. aeruginosa* was found in her stool. The favorable clinical response to polymyxin B was dramatic, and the organism was eliminated from the stool cultures.

SIDE EFFECTS

Some of those given the drug had symptoms which may have been related to its administration. It was difficult to evaluate the part played by psychogenic factors, since no control series with placebos was studied for this purpose. Five had cramps of mild intensity and very variable duration. This usually occurred some time during the first to third day, and lasted for from a few hours to two days. It always stopped in spite of continuation of the drug. Six had slight diarrhea without other symptoms, one had both mild cramps and slight diarrhea, two had mild nausea and slight diarrhea, and 10 were completely asymptomatic.

DISCUSSION

It is apparent that *P. aeruginosa* may inhabit the bowel and produce no symptoms. It may also disappear without therapy. On the other hand, in perhaps 50 per cent of the instances it does not disappear spontaneously over periods of as long as one month. In some cases, it advances from the gastrointestinal tract by invasion of neighboring tissues or via the blood stream and may cause serious and sometimes fatal illness.

Particularly when present in the intestinal tract in large numbers, apparently as a result of an overwhelming inoculation or as a result of suppression of other organisms by drugs, it can become a pathogen. Perforation

* One student, an affiliate, had left the school and no follow-up was possible.

of the bowel wall or metastatic infection of the kidney, central nervous system and other areas may result. Stanley²³ has recently reviewed the rôle of this organism in various infections.

An important consideration is the possible spread from carriers to newborn infants in nurseries. It is clear that epidemic diarrhea of the newborn may be due to this organism.^{12, 15, 16} Not only can it be transmitted in feeding procedures, but it is also known to be transmitted by many preparations such as boric acid, normal saline, acriflavine and penicillin.¹² This study shows that polymyxin B is a reliable drug for the control of such outbreaks.

The polymyxins are bactericidal and have very rapid and effective action.^{18, 21} Polymyxin B in doses approximating those in this study was given orally to children, and after from one to four hours none of the drug was recoverable in the blood or in the urine.¹⁶ Therefore, one need not anticipate toxic symptoms with oral doses such as may be observed with parenteral administration.

Yow²² recently stressed the significance of pseudomonas and proteus infections during or following therapy with other antibiotics. In only one of the subjects had any antibiotic been given within a period of 12 months prior to this study. This was Terramycin, which was given for prophylaxis against psittacosis. In four, however, Sulfathalidine, Sulfasuxidine or sulfadiazine had been taken at some time two to 12 months before pseudomonas was found.

It is becoming increasingly clear that when the commonly used antibiotics or sulfonamides are given, pseudomonas tends to appear in the stool. It also appears from this study that after polymyxin B is given, organisms such as proteus may appear in stool cultures.

In general, side effects were few, mild and of short duration. In some, their relationship to the drug was questionable. Ten of the 26 subjects had no side effects.

In all treated individuals, pseudomonas was eliminated from the stool cultures by the fifth day. In only one could it be recovered again after one month. This of course could have been newly acquired or due to the persistence of the same strain. Unfortunately, the strain was lost before it could be tested for in vitro sensitivity, and this individual was no longer available for reexamination. The organism may have been resistant to polymyxin. The individual had been asymptomatic when the organism was originally discovered.

In view of the possible severity of the disease in infants infected by this organism, it is fortunate that such effective therapy is available for both the carrier state as well as for those with active infection. The organisms, mostly proteus, which were cultured after polymyxin was given usually cleared spontaneously or with administration of sulfonamide.

SUMMARY AND CONCLUSIONS

Polymyxin B was used to treat ambulatory, asymptomatic and symptomatic individuals found to have *Pseudomonas aeruginosa* in the gastrointestinal tract.

In the control group of asymptomatic carriers, about half of the cases were spontaneously free of the organism in the follow-up studies 25 and 30 days later.

One hundred fifty milligrams of the drug were given orally every eight hours for seven days to the experimental group. After five days, all the stools were negative for pseudomonas. Stool cultures were repeated in 23 cases, 25 and 30 days after the drug had been started. At this time, all but one were negative for pseudomonas.

About half of the subjects receiving the drug had mild abdominal cramps or mild diarrhea or both between the first and third days of drug administration, and these lasted from a few hours to two days. They disappeared in each instance in spite of continuation of therapy and without administration of other drugs.

Polymyxin B should be considered promptly as one of the control measures in any outbreak of diarrhea in a newborn nursery where pseudomonas is found as the most likely pathogen. Its use may also be considered as a prophylactic measure when personnel are found to harbor this organism.

Oral polymyxin B is very effective in eliminating *P. aeruginosa* when it is present in the gastrointestinal tract either in carriers or in active infections.

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FUNDAMENTAL CONCEPTS IN THE DIAGNOSIS OF SPRUE*

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SPRUE is a chronic, wasting disease which, in the light of modern medical science, is classified among the deficiency states. Medical literature during the past 20 years has not significantly altered the basic concepts about sprue. Recent observations, however, have contributed materially to a better understanding of the etiologic factors, diagnostic criteria and effective treatment of this interesting syndrome.^{1, 2, 3, 4} In the earlier writings^{5, 6} great importance was ascribed to the differential diagnosis between sprue and Addisonian or pernicious anemia of temperate climates. Mainly through the work of Castle, Rhoads and associates, we now consider these conditions closely related in etiology, symptomatology and treatment.² It is now well recognized and accepted that the condition is a deficiency state amenable to replacement therapy with liver extract, folic acid, folinic⁷ acid and vitamin B₁₂, in addition to a high protein, high vitamin, low fat diet. Improvement includes reversibility of altered gastrointestinal function, of a megaloblastic marrow and of altered metabolism; in other words, improvement in constitutional, gastrointestinal and hematologic symptoms and signs, as well as in laboratory data.

The term sprue is intended to comprise the tropical and nontropical variety (idiopathic steatorrhea). These syndromes are believed to be manifestations or phases of one disease entity. The anatomic and physiologic alterations, the clinical course and response to therapy are believed to be fundamentally similar. It is our impression, however, that occasionally what physicians living in temperate climates have come to diagnose as nontropical sprue or idiopathic steatorrhea is a syndrome secondary to primary gastrointestinal disease, such as abdominal Hodgkin's, lymphosarcoma of the mesentery, amyloid disease, intestinal lipodystrophy and tuberculosis. These conditions may give rise clinically to manifestations of water- and fat-soluble vitamin deficiencies. But the disease entity with which we are concerned in this contribution is a syndrome the etiology and modus operandi of which are still unknown.

In a study by the author of a group of 100 selected cases (57 males and 43 females, ranging in age from 12 to 78 years; 87 white and 13 colored) suffering from uncomplicated sprue, 97 per cent complained of gastrointestinal disturbances which were grouped under the term "dyspepsia." This term comprises (in order of frequency) abdominal distention, epigastric distress (not necessarily related to the taking of food), heartburn and ab-

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dominal discomfort and pain following ingestion of food. Ninety-eight individuals were natives of Puerto Rico, and of the remaining two, one was a male Venezuelan mulatto and the other a continental American who had resided in the island for several years before the onset of sprue. With few exceptions the individuals of this group were of the indigent or underprivileged class, and when seen by us they usually presented a fully developed picture of the sprue syndrome. In over 90 per cent, asthenia, weakness or prostration, diarrhea, loss of weight, carbohydrate and fat intolerance, soreness or pain of tongue and mouth and anorexia occurred. By carbohydrate and fat intolerance we mean the aggravation of gastrointestinal symptomatology, particularly diarrhea, following ingestion of rice, beans and fried foods. These articles of diet are consumed in large quantities in the daily menu of Puerto Ricans. Gastrointestinal disturbances constituted the earliest subjective manifestations of sprue in the group studied. As a rule they did not appear following a dietary indiscretion or alcoholic abuse. Flatulence, eructation, heartburn, meteorism and diarrhea, as mentioned above, were made worse with the ingestion of rice and beans, cereals, bread and potatoes and fried foods in general. Curiously enough, these foods are not excluded from the daily fare until later, when the tongue and mouth are too sore and painful to tolerate even water. Indigestion may persist for months before the more disabling and aggravating symptoms ensue, but soreness of the tongue or mouth accompanied by looseness of the bowels appears after two or more months of dyspepsia. Watery, frothy, yellowish, fermentative, acid stools, occasionally grayish or light colored, which may or may not be ushered in by tenesmus or cramplike pains, soon dominate the picture. Movements are almost constantly preceded by an imperative desire to go to stool, and not infrequently stools are passed involuntarily before the patient is able to reach the toilet. Their frequency is quite variable, ranging from two or three to 20 motions or more during the day. The number of stools occurring during the day is far higher than those occurring at night. One to three movements before breakfast in the early hours of the morning are characteristic. As diarrheal stools are precipitated by ingestion of foods, particularly in the solid state, the patient, though hungry, is afraid to eat and soon loses appetite and is repelled by the sight and odor of food. Soreness and pain of the tongue and mouth progress, complicating the clinical picture, and from then on loss of weight and strength is rapid. A loss of 50 pounds in four to six months in a person normally weighing 120 to 130 pounds is not infrequently seen.

Palpitation, with dyspnea on exertion and vertigo, and headache occurred in 58 and 48 per cent of the individuals, respectively. Tenesmus, burning or pain associated with the passage of stools was present in 35 per cent. Stools containing mucus or blood were reported by 20 per cent. Tarry stools and fresh blood in the absence of hemorrhoids were observed in some cases. In 20 per cent intermittent diarrhea with variable periods of con-

stipation was observed. Nausea or vomiting, usually following ingestion of food, occurred in 17 per cent. Nervousness, irritability and insomnia were reported in 15 per cent. Neurologic symptoms such as numbness of toes and fingers, formication and paresthesias were noticed in 14 per cent.

Menstrual disorders, usually amenorrhea, leukorrhea or both, were complained of by 8 per cent of the females. In the majority of cases these symptoms disappeared during treatment.

Physical examination revealed as its most striking finding a marked degree of muscular wasting or cachexia. Malnutrition, emaciation or cachexia was found in 80 per cent of the individuals. The rapid loss of weight, with its pitiful wasting of tissues in a comparatively short time, is characteristic of acute sprue. In chronic cases, when cachexia has advanced to a maximum compatible with life it seems to reach a standstill, and the unfortunate beings drag themselves around showing a true "skin and bones" appearance. It is surprising, however, to watch the degree of activity some of them display, going on their way with a million red cells per cubic millimeter and looking like ghosts. This apparently effortless activity is a contrast to that of patients with hookworm disease and anemia, who may have anywhere from 3 to 4 million red cells per cubic millimeter, yet exhibit great effort in moving about; their actions are sluggish, and dyspnea on the slightest exertion is obvious. However, their hemoglobin is much lower (20 to 30 per cent; 2.9 to 4.4 gm.) in proportion to the number of red cells, the reverse of that which usually occurs in sprue.

Glossitis and stomatitis were present in 94 per cent. Various degrees of involvement of the tongue were encountered, from the fiery red, beefy, glossy appearance with or without desquamation and atrophy of the papillae (60 per cent), with excoriation of the surface and borders seen in acute cases, to the smooth, grayish, dull, pale organ, completely devoid of papillae and characteristic of chronic cases (34 per cent). Stomatitis with patchy involvement of the buccal mucosa and of soft palate was the most prominent mouth lesion. No ulceration of lips or of the margins of the mouth (cheilitis) was observed. Aphthae on the surface of borders of the tongue and on the buccal mucosa were found in only 16 per cent. A greater frequency of these lesions was to have been expected.

Pallor of the skin, usually generalized, occurred in 70 per cent. In white individuals a lemon tint of the skin of the face and the forehead was frequently present. In others, the skin assumed a dull gray or dirty yellow, parchment-like appearance, reminiscent of a mummy. True pallor of the skin in white individuals living in the tropics is difficult to discover because of sun tanning. Other skin changes were observed in 63 per cent of cases. These consisted mainly of areas of brownish hyperpigmentation with roughening, located (in order of frequency) on the forehead, cheeks, extensor surface of the forearms, anterior and posterior aspects of the neck, and anterior surfaces of the legs. These lesions were invariably symmetrical

and of various sizes and intensity of color. They were usually dry, and often presented discrete borders, slight atrophy and wrinkling of the skin, with scaling resembling ichthyosis. The hair of many patients, particularly those below 30 years of age, was fine, dry, scant in the axillae or pubis, and lacked luster.

Occasionally the changes in the skin were similar to pellagroid lesions, but no erythema or ulcerations were observed. No petechiae or purpuric spots were seen. Cheilitis was not encountered in this series of cases. Edema was present in 40 per cent, the most frequent sites being the feet and ankles. Rarely was edema of the face, ascites or general anasarca observed. Hospitalized patients (University Hospital, School of Tropical Medicine, San Juan, Puerto Rico) offered ample opportunities for the study of pyrexia not related to infection. Thirty-seven per cent of all cases showed elevated temperatures when first seen. The majority of the 27 individuals admitted to the wards had some degree of fever on admission and during sojourn in the hospital. As a rule the fever was remittent in type, with rises to 101° or 102° F. in the evening and remission to normal or subnormal values in the morning. Fever receded by lysis as the clinical condition improved. Subnormal temperatures as low as 95° F. are reported in some individuals before improvement begins.

Neurologic changes occurred in only 10 per cent. These consisted mainly in diminution or absence of tendon reflexes, and absent or diminished vibratory sensation at the malleoli, dorsum of feet, and along the legs to the iliac crests. No ataxia was encountered in any case.

Icterus of the sclera or of the skin was observed in 10 per cent of the cases. Usually it was correlated with increased bilirubin in the blood.

Cardiovascular disturbances such as heart murmurs, apparently hemic in character, coldness of the extremities, and arteriosclerosis of peripheral arteries in some of the elderly individuals, were observed in 10 per cent of the cases. Blood pressure readings were usually low, the systolic values rating from 80 to 120 mm. and diastolic between 30 and 60. The shape of the heart to the x-ray was sometimes described as of "hanging drop" appearance.

Anemia of variable intensity and of several types was encountered in all individuals. In no instance were normal values for hemoglobin or red cells found. The mean erythrocyte count for the entire group was 2,510,000 red cells per cubic millimeter, the lowest and highest being .84 and 4.47 millions, respectively. The mean hemoglobin for the group was 9.77 gm., and the values ranged from 3.7 to 16 gm. In 90 per cent of the cases a macrocytic hyperchromic anemia, with a mean corpuscular volume of 119 cubic microns and a mean corpuscular hemoglobin of 34 micro-micrograms, was observed. The normocytic type was reported in 7 per cent, simple microcytic in 1 per cent, and hypochromic in 2 per cent of the cases.

Free hydrochloric acid was present in 95 per cent. In 60 per cent of

these acid was recovered following Ewald's meal, and in 35 per cent following alcohol or histamine stimulation. Hypochlorhydria was a frequent finding in those showing free acid. Hyperchlorhydria was not reported in any case.

Reference has already been made to the number, corpuscular volume and hemoglobin content of the peripheral red cells. Studies of the leukocytes and platelets have also been performed, and have shown a leukopenia and thrombocytopenia in many cases. Determination of bleeding and coagulation time, fragility of the red cells and clot retraction were performed in some cases. All of these tests gave results within normal limits.

Stools: The amount, consistency, color, odor and chemical composition are affected. We believe the normal stools of the rice-eating people of Puerto Rico to be unduly large and bulky. In sprue, however, a small stool passed with much gas is typical. This is probably due to the fact that the usual liberal amounts of rice, beans and undigestible material in the diet have been avoided, and to the frequency of bowel movements. Watery, foamy, fermented dejections with an acid or sour odor are characteristic of acute sprue. An offensive, putrid foul odor was frequently encountered, particularly in chronic cases. The reaction is strongly acid. When the patient is fed a suitable diet and administered liver extract the stools soon become semisolid, the odor changing to that of normal movements. Semi-solid stools may persist for months or years before formed, normal movements are passed. As to the color, we must admit that the copious, pale, grayish, fatty, foul stool, described in the literature as typical of sprue, has been rare in our experience. A bright yellow, golden or brown stool, mixed with variable amounts of foam, is the rule. We have seen tarry stools in some cases of sprue, as well as fresh blood, and 20 per cent of the cases stated that they have passed blood or mucus. As to the chemical composition of the stools, it has been shown by Asenjo * that only 30 per cent of sprue cases were found to have steatorrhea, that is, increased percentage of fat in dried feces. However, fat absorption studies demonstrated a significant impairment of fat absorption in five out of seven cases studied.

Urine: No pathologic changes in the urine were found in this series of cases. In some patients a low grade genitourinary infection such as cystitis or prostatitis may be encountered, but this is to be considered a complication. A few patients complain of marked nocturnal polyuria, that is, during the period when bowel movements are less numerous. The significance of this observation is not known, but it is the subject of current investigation.

Blood Chemistry: Studies in blood chemistry were as follows: The blood glucose was found within normal figures but the results usually fell below 100 mg. per 100 c.c. of blood, usually around 80, occasionally around 70, the lowest 68 mg. As expected, oral glucose tolerance tests showed a flat type of curve in 90 per cent of the cases, which is considered characteristic

of the sprue syndrome. Urea nitrogen and nonprotein nitrogen determinations were normal, as were the uric acid and creatinine. Total plasma proteins fell within normal variations except in cases with edema, in which the results were invariably below 5 gm. per cent. Values between 5 and 5.5 per cent were frequent. Low plasma protein levels indicate, of course, an abnormal state of nutrition, which may be correlated with the rapidly wasting tissues seen in sprue. The albumin and globulin fractions were reduced without disturbance of the proportion between the two. One middle-aged female showed 2.2 gm. per cent of total proteins. She had general anasarca with marked edema of the lower extremities and ascites, which at first was thought to be due to a blockage of the pelvic venous circulation. Under liver extract and high protein, low fat diet, the plasma proteins rose to 6.5 per cent within two months and the edema disappeared completely.

Cholesterol determinations showed low values, the highest being 133 mg. per cent and the lowest, 90 mg. per cent.

The chlorides (whole blood) fell within normal variations and below normal in some individuals.

Icteric indices were usually observed below 6 units, but in three instances they were increased, the highest result being 14 units. The serum bilirubin in this case was as determined by the van den Bergh test, 0.95 unit.

Calcium and phosphorus determinations showed normal figures. However, values between 8.5 and 9 mg. per cent for the calcium and 2.5 to 3.0 mg. for phosphorus were common. The question of what constitutes normal calcium and phosphorus values in a country where the daily per capita intake of calcium is low requires further investigation. It is opportune to mention that in no case were there clinical manifestations of calcium or phosphorus deficiencies. No evidences of osteoporosis or osteomalacia were discovered.

The determination of basal metabolic rates showed normal values.

DIAGNOSIS

The diagnosis of sprue was comparatively simple in the group studied. In the majority of cases a correct diagnosis was arrived at from the chief complaints alone. On the other hand, this series comprises a particular type of individual in whom the classic features of the disease in full bloom were observed when the patient received medical attention. We realize, however, that in private practice diagnosis may be difficult, as anemia may be present without marked lingual or intestinal symptoms, or vice versa. Likewise, gastrointestinal disturbances including diarrhea may be mild.

We believe the diagnosis of the sprue syndrome is based upon the following criteria:

1. Insidious onset, chronicity of symptoms, and paucity of spontaneous remissions.

2. Presence of stomatoglossitis, with or without atrophy of the lingual papillae.
3. Gastrointestinal disturbances ("dyspepsia," diarrhea and steatorrhea).
4. History of recent weight loss, accompanied by increasing weakness and prostration.
5. The presence of free hydrochloric acid in the stomach in a high percentage (over 90 per cent) of cases.
6. The presence of a macrocytic, hyperchromic anemia, associated with a megaloblastic marrow.
7. A flat glucose tolerance curve (oral).
8. Absence of neurologic manifestations in the majority of cases.
9. Hyperpigmentation of the skin, particularly the face, arms and legs.
10. "Inflammation" * and atrophy of the gastric and rectosigmoid mucosa.

Difference in degree of intensity and in frequency of these symptoms and signs may be quite variable in different individuals, but in our experience during the past 20 years a general uniformity about the clinical picture has been the rule, particularly so in the present group of patients.

Some of the differences existing between sprue encountered in the tropics and that observed in temperate zones are, first: clinical manifestations of hypocalcemia are frequently observed in sprue occurring in cold climates, but are seldom encountered in the tropics. Bone changes such as osteoporosis and osteomalacia associated with low serum calcium levels are rarely observed in sprue occurring in tropical areas. Second: hypoprothrombinemia is encountered more commonly than in sprue occurring in the tropics. Third: the management and therapy offer greater difficulties in non-tropical sprue; response to therapy is not as rapid or as effective.

Observation of the natural history of sprue during several years has prompted the present author to postulate the following mechanism of this peculiar disease. (The mechanism or mechanisms involved in bringing about the sprue syndrome remain as yet obscure.)

The underlying pathologic physiology in the syndrome is primarily related to the small intestine, presenting itself as a small bowel dysfunction, that is, a defect of intestinal absorption. This derangement of the gastrointestinal system occurs early in the course of the disease and is manifested clinically by gastrointestinal disturbances which may (and often do) precede the presence of anemia. At some time during the course of the disease, but probably during the active phase, this defect in intestinal absorption is accompanied anatomically and grossly by hyperemia and edema of the intestinal wall, and by marked distention of the gut; histologically, by atrophy of the mucosa of jejunum and ileum and degenerative changes in Auerbach's plexus; physiologically, by inability of the intramural nervous apparatus of

* For lack of a better term, "inflammatory" has been employed to describe the appearance of tongue and mouth lesions. We do not believe these changes are to be regarded as inflammatory in nature, that is, as produced by an infectious agent.

the intestine to produce acetylcholine; clinically, by a variety of subjective and objective gastrointestinal disturbances; roentgenologically, at first by hypermotility of the bowel, and later by hypomotility, delayed passage of barium through jejunal and ileal loops, abnormal segmentation and coarsening of the folds, or the so-called "moulage" sign. These changes are usually, though not invariably, associated with the presence of a macrocytic hyperchromic anemia, leukopenia and thrombocytopenia, a hyperplastic marrow with a megaloblastic increase, a low or flat glucose tolerance curve, low serum protein values, and an increase in split fats in the stools (steatorrhea). Many of these alterations are reversible, depending, of course, on the severity of the syndrome.

Now, one naturally inquires about the circumstances or factors that give rise to or initiate the course of events we have first mentioned. At present, our knowledge points to a dietary deficiency in animal proteins and fresh vegetables, a multiple deficiency, if you will; a deficiency maintained during a variable but still undetermined period of time. In addition to the evidence obtained from Castle's ingenious experiment, the broad concept of dietary insufficiency is supported by epidemiologic evidence, such as the occurrence of a spruelike syndrome in population groups affected by famine or by chronic starvation; or when an inadequate dietary is present, as that which prevails among certain prisoners-of-war, in concentration camps, or during periods of national economic crisis. It also correlates well with a history of dietary deficiency in many individuals independent of their economic status, and preceding the onset of sprue.

With the available clinical and laboratory evidence at hand we can now restate and reemphasize what Thaysen⁹ said several years ago, that pernicious anemia, sprue (tropical and nontropical), celiac disease, nutritional macrocytic anemia and pellagra are closely related and allied diseases, probably having a common denominator, yet differing significantly in the body systems affected and in the emphasis by which they are so affected. In all these conditions gastrointestinal abnormalities, anemia and nervous manifestations are encountered, but the emphasis of such symptoms is very differently placed. Thus, in a general way the derangement of the gastrointestinal system is more severe in sprue and in celiac disease than in pernicious anemia or pellagra; while on the other hand, dysfunction of the nervous system affecting spinal and cerebral pathways is observed more frequently and is involved more severely in pellagra and in pernicious anemia.

In closing, a word must be said regarding investigation now in progress. The rôle of the adrenocorticotrophic hormones in the study of gastrointestinal absorption in sprue occurring in the tropics is the subject of current investigation. Preliminary observations* include improvement of gastrointestinal manifestations and glucose absorption following short periods of administration of ACTH by intravenous route. The significance of such observations, however, remains as yet unexplained.

* Dr. Agustin M. de Andino: personal communication.

SUMMARY

1. A clinical study of 100 uncomplicated cases of sprue is included. The clinical picture is analyzed and the percentage of different symptoms and signs encountered is presented.

2. The material for study comprised 57 males and 43 females, ages ranging from 12 to 78, with a mean age of 40.14 years. There were 87 white and 13 colored individuals, including two full-blooded Negroes. The white group was composed of Puerto Ricans of Spanish extraction and one white North American.

3. Laboratory data, including blood findings, gastric analysis, stools, urine, blood chemistry and basal metabolic rates obtained in these cases, are presented.

4. A discussion is given of the fundamental concepts in the diagnosis of sprue, including the criteria which, in the author's opinion, must be present to arrive at the diagnosis of this condition.

5. Some of the differences existing between sprue observed in tropical areas and that encountered in the temperate zone are discussed.

6. The mechanism or *modus operandi* of the sprue syndrome is discussed.

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CARDIAC WORK AND THE CHAIR TREATMENT OF ACUTE CORONARY THROMBOSIS *

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INTRODUCTION

IN the past two years there has been considerable interest in and much discussion of the "chair treatment" for acute coronary thrombosis. This interest and discussion was stimulated principally by the observations of Levine,¹ who has questioned whether the recumbent position in bed is the optimal posture for putting the heart at rest. His clinical observations and those of others have indicated that patients with acute coronary thrombosis often get along better when allowed to sit up in a chair than when kept in bed.

Complete bed-rest has been stressed in the therapy of acute coronary thrombosis since Herrick's² first clinical description of "sudden obstruction of the coronary arteries." In the years since Herrick's report many drugs and measures have been added to the therapeutic regimen of acute coronary thrombosis, but bed-rest has remained the cornerstone of management.

There has been some confusion, perhaps, in the minds of clinicians concerning Levine's "chair treatment." He suggested this method in the belief that the chair posture afforded the injured heart a greater opportunity to rest than did the usually prescribed recumbent position. The "chair treatment" is not to be confused with the concept of early ambulation. To emphasize this, it is pointed out that the patient is to be transported from the bed to the chair with a minimum of effort on the patient's part.

The present study was undertaken to determine the actual work of the heart in the armchair position as compared to the resting, recumbent position.

METHOD OF STUDY

Six patients from the Medical Wards of the Louisville General Hospital were studied (table 1). The first two patients (D. C. and W. C.) were convalescing from acute infections, the third (W. P.) was a controlled epileptic. These first three had normal cardiovascular systems. The last three (J. G., E. E. and W. W.) were diagnosed as cases of arteriosclerotic heart disease.

The last three had enlarged hearts by telerradiography, and all had abnormal electrocardiograms compatible with the diagnosis of coronary artery disease. Patient J. G. was mildly decompensated at the time of study.

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Patients E. E. and W. W. were in moderate failure at the time of study. Each patient was studied while in the basal state.

The patients were allowed to rest for 45 minutes in the recumbent position on a heavily padded fluoroscopy table. The last three patients all required two standard pillows under the head for comfort.

A cardiac catheter was then placed in the pulmonary artery by the usual technic.³ As soon as the patient was in a "steady state"⁴ a cardiac output determination was made by the dye injection method.^{5,6} The dye (T 1824) was injected into the pulmonary artery and serial arterial samples were obtained from an indwelling radial artery cannula. Intra-arterial pressures were obtained from the radial artery by means of a Cambridge electro-manometer.

The patient was then helped into a padded armchair, where he remained for 30 minutes, and the cardiac output and pressure measurements were then

TABLE I
Description of Six Patients Studied

Patient	D. C.	W. C.	W. P.	J. G.	E. E.	W. W.
Sex	M	M	M	M	M	M
Age (yrs.)	18	36	50	56	67	78
Height (cm.)	171	174	165	153	173	183
Weight (kg.)	68.4	65.9	71.3	42.5	55.5	63.6
Surface Area (m ² .)	1.8	1.78	1.8	1.34	1.65	1.83
X-Sec. Area Aorta (cm ² .)	2.2	3.0	3.9	2.9	4.0	4.6

repeated. None of the six patients demonstrated any evidence of anxiety during the studies conducted.

The cross-sectional area of each patient's aorta was obtained from the graphs developed by Bazett et al.⁷ based on the subject's age and body surface. This area, as indicated later, is used in the formula for cardiac work.

CALCULATIONS

The mean arterial pressure was measured by planimetric integration of the area beneath the pulse pressure tracings obtained with the Cambridge electro-manometer and the Sanborn four channel poly-viso.

The mean circulation time was obtained from the dye concentration-time curves, and is the time required for one-half of the dye to pass from the point of injection to the point of sampling.

The pulmonary blood volume was calculated by multiplying the cardiac output per second by the mean circulation time. Although this volume of blood is commonly referred to as the pulmonary blood volume, it actually represents the volume of blood in the vascular compartment from the point of injection of the dye to the point of sampling, and therefore includes the left side of the heart and part of the arterial system.

Peripheral resistance was calculated by the formula $R = \frac{P_m \times 1332}{V_t}$, where P_m is mean arterial pressure in millimeters of mercury and V_t is cardiac output in cubic centimeters per second. The number 1332 in the formula is a constant.

Cardiac work was determined by the application of the formula $W = QR + \frac{MV^2}{2g}$, where R is the mean blood pressure or resistance; Q , the volume of systolic discharge; M , the mass of ejected blood; V , the velocity, and g , gravity or 980 cm. per second squared.

M , the mass of the ejected blood, was obtained by multiplying the volume of systolic discharge by the specific gravity of blood, 1.056. V , the velocity of the ejected blood, was calculated by dividing the cardiac output per second by the cross-sectional area of the aorta and squaring the result.

If the calculation is made as described the cardiac work is determined in the units, grams centimeters per beat. This figure may be converted to work, in terms of grams centimeters seconds by multiplying by the cardiac rate and then dividing by 60.

RESULTS

It can be seen in table 2 that when the patient assumes the armchair position there is usually a slight increase in heart rate and a prolongation of the mean circulation time. In four of the six patients there was a diminution in the calculated pulmonary blood volume. This was most marked in patient E. E., where the change in this volume amounted to 685 c.c. and correlated well with the prompt relief of respiratory distress that this patient noted when he sat up in the chair.

There was a small increase in the hematocrit in the armchair position. In each patient the stroke volume was smaller in the armchair position. The mean arterial pressure changed very little when the armchair position was assumed.

In each instance the calculated peripheral resistance was greater in the armchair position. The mean reduction in the cardiac index in the armchair position amounted to 0.73 L. per square meter of body surface, or 21 per cent. The calculated cardiac work in each patient was less in the armchair position than in the recumbent position. The mean reduction in work amounted to 2,787 gm. cm. per second. This represents a 23 per cent reduction of cardiac work in the armchair position.

DISCUSSION

In the past a number of studies have been directed toward the effect of the erect posture on the cardiovascular and respiratory systems. However, none has studied the armchair position specifically. Waterfield¹⁰ found the blood volume to be less in the erect than in the recumbent position. This

TABLE II
Response of the Cardiovascular System to the Armchair Position as Compared to the Resting Recumbent Position

Patient	D. C.		W. C.		W. P.		J. G.		E. E.		W. W.	
	Res	Ar	Res	Ar	Res	Ar	Res	Ar	Res	Ar	Res	Ar
Cardiac rate	90	94	66	72	92	96	78	80	112	108	54	58
Mean cir. time (sec.)	10.2	11.4	12.4	14.2	12	12.6	13	15	26.2	27.4	30	50.4
Cal. pul. blood volume	1,327	1,387	1,609	1,668	1,067	756	1,205	1,060	2,237	1,552	1,828	1,732
(c.c.)												
Stroke volume (c.c.)	87	79	118	98	59	38	71	53	45	32	67	36
Hematocrit	32	32	40.4	40.5	40.5	43.1	41.2	41.5	36.9	37.4	44.9	46.4
Cal. per. res.	768	812	789	831	1,588	2,500	1,174	1,445	1,724	2,113	1,507	2,664
(dynes sec./cm. ²)												
Mean art. pressure	75	75	77	73	106	115	82	77	110	92	69	68
(mm. Hg)												
Cardiac output (c.c./min.)	7,780	7,389	7,786	7,052	5,335	3,603	5,563	4,240	5,125	3,472	3,656	2,062
Cardiac index (liters/m ²)	4.3	4.0	4.3	3.9	2.9	2.0	4.1	3.1	3.1	2.1	1.9	1.1
Cardiac work	9,405	8,599	12,954	10,359	8,579	6,213.5	8,329	5,878	7,191	4,235.5	6,716.1	3,561
(gm. cm./beat)												
Cardiac work	14,107	13,471	14,249	12,430	12,821	9,941	10,826	7,837	13,423	7,623	6,044	3,442
(gm. cm./sec.)												

* Mean for the 6 patients studied. + indicates an increase in the armchair position. - decrease in the armchair position.

loss in blood volume was mainly in the plasma fraction, and amounted to 15 per cent of the total plasma volume.

Perera and Berliner¹¹ have shown that hemoconcentration occurs in the standing position. Associated with this is a rise in serum proteins resulting primarily from the loss of fluid from the circulation. These two investigators have noted that a significant change in the serum protein concentration can occur in a few minutes, although a longer period is required for a maximal effect.

McMichael and McGibbon¹² found that in the recumbent position the total volume of air in the fully expanded lungs decreases by 340 c.c. on the average. This decrease is not associated with any measurable diminution in the size of the thoracic cage, and is therefore presumably due to an increase in the pulmonary blood volume in the recumbent position.

Thompson et al.¹³ found that in the standing still position there is a net loss of approximately protein-free fluid from the blood. This loss amounts on the average to about 11 per cent of the total plasma volume. A decrease in cardiac output in man on changing from the reclining to the standing posture has been reported by Lindhard,¹⁴ McMichael and Johnston¹⁵ and Bazett et al.¹⁶

We believe the response of the cardiovascular system to the armchair position is the same as that to the standing position, although the changes may not be so marked. The question might be asked as to what happens to coronary blood flow in the armchair position. This would of course be particularly pertinent in the patient with acute coronary thrombosis.

The coronary blood flow varies directly with the size of the vascular bed, the pressure head and, inversely, with the back pressure at the end of the system and the viscous resistance encountered in transit through the entire bed.¹⁷ The aortic blood pressure determines the pressure head applied at the coronary orifices. In the six patients studied the arterial pressure changed very little when the armchair position was assumed.

The right atrial pressure represents the back pressure at the end of the coronary system. Although atrial pressures were not determined in this study, we have evidence from some studies of Warren et al.¹⁸ that the right atrial pressure would fall as the subject approaches the upright posture and venous pooling occurs in the extremities. The size of the coronary vascular bed would not be expected to change by the patient's assuming the armchair posture, nor would the viscous resistance be expected to increase. Therefore, it is probable that the coronary blood flow is not reduced by putting the patient in the armchair as compared to the recumbent position in bed. It may even be increased by approaching the upright position as long as there is no postural hypotension.

There are some contraindications to the "chair treatment." One of these would be the presence of shock. Another would be symptoms of cerebral ischemia in the armchair position. One must be sure that the armchair does

not unduly compress the popliteal space and predispose to venous thrombosis in the legs. Also, there is the danger that the patient allowed up in a chair may take his condition too lightly and undertake unauthorized activities. This must be guarded against by the proper explanations to the patient. Levine¹ has already pointed out that patients with acute coronary thrombosis given the "chair treatment" have fewer bowel and bladder complications, and that the chair encourages a more hopeful attitude toward this serious illness.

SUMMARY

In six patients the cardiac work was determined in the resting recumbent position and again with the patient in an armchair. In each patient the calculated cardiac work was less in the armchair posture. The mean reduction in the work of the heart amounted to 23 per cent. This gives support to the clinical observations of Levine¹ that patients with acute coronary thrombosis are often benefited by the "chair treatment."

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EMOTIONAL STRESS BEFORE STROKES: A PRELIMINARY REPORT OF 20 CASES*

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PRECEDING a cerebral stroke the patient has often suffered long-standing progressive difficulty in settling emotional problems. Immediately before the stroke he may have faced an overwhelming personal threat. Such life situations, in which the stroke occurs, have usually been overlooked, perhaps because the physician has been absorbed in the physical features of the case. Except for the occasional reference to anger immediately preceding apoplexy, medical literature has generally been silent about the association of stroke and previous emotion. Nevertheless, the pertinent facts can usually be brought out by the physician who inquires into the social and personal history.

The purpose of this preliminary report is to present a series of 20 cases illustrating the association between cerebral stroke and preceding emotional stress. It is not claimed that such emotional settings are the only factors implicated in cerebral strokes, but they may prove to be contributory. If this is true, cerebral vascular "accidents" would not be entirely accidental.

The cases of this series have been selected from those referred for neurosurgical consultation in the last few years. They include all the examples of both nontraumatic intracranial hemorrhage and sudden hemiparesis in which an adequate personal history was obtained. In the average case this information was gathered in about an hour. Usually, general and neurologic studies were carried out first and the pertinent personal history was obtained later.

CASES OF NONTRAUMATIC INTRACRANIAL HEMORRHAGE

Intracerebral Hematoma, Left Occipitotemporal

Case 1. A 25 year old male had experienced left frontal headache for the past five months; it had been worse in the past six weeks. Two days before admission he had had a very severe left frontal headache, transitory anomia, alexia and intermittent fever. *Examination:* Tenderness in left temporoparietal area, unsteadiness of gait, transitory anomia and alexia. Visual fields normal. *Electroencephalogram:* Left temporo-occipital focus. *Left carotid angiography* and *pneumoencephalography* revealed an avascular cystic mass in the left occipitotemporal region. *Craniotomy* disclosed an intracerebral hematoma the size of a hen's egg 3 mm. beneath the surface of the cortex. Recovery was essentially uneventful, except for an occasional convulsion.

Pertinent personal history was obtained six months after operation, when the patient's confidence in the physician had been fully established. Before the present illness, the patient was being investigated for possible sterility. An attempt to produce a specimen of semen in the office of a urologist had been a failure on two previous

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occasions. On the date scheduled for the third visit to the urologist for the same purpose, the patient became extremely anxious and had the first severe headache, which marked the onset of the present illness. The inability to produce semen on the two previous occasions and the possibility of failure at the third appointment was the greatest personal threat the patient had experienced in his life.

Hemorrhage into Basal Ganglia

Case 2. This 11 year old girl failed to find her mother at home one day, became frantic, ran from house to house and finally collapsed. Bloody spinal fluid and left hemiplegia were found. *Angiography* was technically inadequate. *Pneumoencephalography* revealed marked enlargement of the right basal ganglia and hydrocephalus. This test was repeated one month later and revealed atrophy of the right thalamus and parieto-occipital region of the right cerebral hemisphere.

Spontaneous Subarachnoid Hemorrhage without Aneurysm

Case 3. A 33 year old female had suffered sudden right hemiplegia and aphasia. Spinal fluid contained 5,000 erythrocytes per cubic millimeter. *Angiography* at first revealed spasm of the internal carotid artery and, five months later, normal arteries. The patient suffered another stroke a year to the day after her first. The second stroke proved fatal. *Autopsy* revealed that the blood vessels of the brain were normal.

Pertinent personal history has been given in detail elsewhere.^{1, case 1} The first stroke followed failure of the patient to manage her life under conflict with her mother. The second stroke occurred as she was about to strike her daughter.

Case 4. A 16 year old boy had sudden onset of headache, vomiting, stiff neck and lethargy. Spinal fluid was grossly bloody. Right and left *carotid angiography* and indirect *vertebral angiography* revealed no aneurysm, but there was definite variation in caliber of the branches of the left middle cerebral artery in successive arteriograms. The patient did well for four years, at which time he returned for routine check-up, free from signs and symptoms.

Pertinent personal history: At the time of reexamination the patient recalled that the subarachnoid hemorrhage four years previously had been immediately preceded by the following episode: An older boy had moved into the neighborhood and taught the patient to masturbate. Sometimes the patient failed and sometimes he succeeded, but he always felt a sense of guilt.

Case 5. A 68 year old man had been known to be diabetic for 10 years and to have some cardiac disorder, as a result of which he lived a very calm life. An escaped convict forced him at knife's point to drive rapidly over the highways for an hour. Within a few minutes of being released the patient suffered severe headache, nausea and vomiting. A few hours later he became confused and developed right hemiplegia. He was hospitalized and the right arm was found to be flaccid, the right lower limb spastic. There was absence of the tendon reflexes on the right side, and Babinski's sign was present on both sides. Death occurred 16 hours after his release by the convict. *Necropsy* revealed subarachnoid hemorrhage in the region of the chiasmal cistern. A careful examination of the circle of Willis and its branches revealed no evidence of aneurysm or of advanced arteriosclerosis. There was no other abnormality in the brain.

Case 6. A 48 year old woman was found unconscious in the bathroom. Spinal fluid was bloody. There were subsequent drowsiness and vomiting. *Angiography* revealed definite spasm of the intracranial portion of the left internal carotid artery. There were progressive restlessness and somnolence. Death occurred 15 days after admission. *Necropsy* revealed brownish staining of the arachnoid at the base of the brain. Careful study of the cerebral blood vessels revealed neither aneurysm nor

thrombosis. *Microscopic examination* revealed widespread areas of demyelination, which could have resulted from ischemia.

Pertinent personal history was obtained from relatives. The patient had been a tomboy, and competed with men in the office where she worked. She had never married. She had anxiety attacks and began to display hostility toward her sisters. The psychiatric aspects have been discussed in more detail elsewhere.^{1, case 2}

Case 7. A 39 year old man had a sudden onset of headache, followed by stiffness of the neck and the discovery that the spinal fluid was bloody. Except for signs of meningeal irritation, the neurologic examination was negative. *Angiography* revealed marked narrowing of the entire circle of Willis, which is strong presumptive evidence of spasm.

Pertinent personal history was obtained from the patient a few months later. He had been a wanderer in his youth and had had difficulty establishing relations with girls. Psychiatric study indicated that the patient had a schizoid personality with paranoid trends. He felt trapped in a home situation, which was dangerous for him.^{1, case 4}

Case 8. A 20 year old girl began to have headache, nausea and vomiting at the time of a menstrual period. The spinal fluid was found to be bloody. The gait was awkward, the neck rigid and the left sixth cranial nerve weak. Babinski's sign was present on the left. The rest of the neurologic examination was normal. Carotid *angiography* revealed spasm in the right internal carotid artery near its bifurcation, and of the right anterior cerebral artery shortly after its origin. Studies for hemorrhagic diathesis were negative.

Pertinent personal history: The patient had been a tomboy and had had dysmenorrhea, as had her mother. She had an immature relationship with boys. Further psychiatric data have been presented elsewhere.^{1, case 5}

Subarachnoid Hemorrhage with Aneurysm

Case 9. A 39 year old man had a sudden headache with severe pain back of his left eye. The cerebrospinal fluid was bloody. A second subarachnoid hemorrhage occurred two months later. At this time, *angiography* revealed an aneurysm at the juncture of the right anterior cerebral and anterior communicating arteries. Subsequent arteriograms revealed localized variability in caliber of the right sylvian arteries.

Pertinent personal history was obtained a year and a half later. The patient had always restrained his temper and avoided arguments. Although he had asthma, he tried to deny his physical limitations by excessively vigorous physical activity.

A month before the first subarachnoid hemorrhage the patient's wife had had a "nervous breakdown," and the patient feared she might become insane. This anxiety persisted even after the wife came home. The husband used to do a day's work and then go home to do washing and other chores to keep the house going. He became more and more worried and tired, and had a feeling of being cornered. It was at this time that the subarachnoid hemorrhage took place. A month later his father died suddenly, and immediately following this the patient had a severe headache. After another three weeks he had his second subarachnoid hemorrhage, which was followed by *angiography*.

Two months' bed-rest were prescribed. After two weeks' bed-rest in the hospital, on the night before he was to go home, he suffered an extremely severe exacerbation of his headache. This resulted in his not going home until the end of a two-month period.

Case 10. A 32 year old woman had suffered severe headache of sudden onset two weeks previously. The headache continued and became exacerbated on the day of admission. *Examination* revealed stiffness of the neck, impaired straight-leg raising, drowsiness and Babinski's sign. The cerebrospinal fluid was grossly bloody and

under normal pressure. *Angiography* revealed a saccular aneurysm extending posteriorly from the right carotid artery in the region of the origin of the posterior communicating artery. There was localized variability in caliber of both the horizontal and the vertical portions of the right anterior cerebral artery, as seen in successive arteriograms.

Pertinent personal history was obtained a year later. She had married late in life, and competed with men in a man's job. She was overprotective of her mother and sister. The patient had been sterile for two years before the onset of the present illness, and was found to have a small uterus. A year before the subarachnoid hemorrhage her sister had undergone removal of a breast, and this had been a shock to the patient. Four months before the present illness a brother had had difficulty with his marriage. At about this time the patient was greatly depressed because she had been counting on cortisone to help her arthritis and it had failed to do so. She began to feel guilt toward her husband, not only because of her sterility but also because she felt she was an inadequate sexual partner.

Case 11. A 37 year old man had sudden onset of pain radiating from the neck and shoulder to the occiput. The following day partial *left* oculomotor palsy developed which lasted five months. At the time of the onset of headache, bloody spinal fluid was found. Later the patient developed *right-sided* facial and cranial pain. *Neurologic examination* a year after the onset of the illness was entirely normal except for residual partial left oculomotor palsy and left trochlear palsy. *Right and left carotid angiography* and indirect *vertebral angiography* revealed a tiny aneurysm along the subarachnoid course of the *left* internal carotid artery. There was also marked evidence of active change in the caliber of the *right* internal carotid artery and its branches.

Pertinent personal history was obtained a year and a half after the angiogram, that is, two and one-half years after the subarachnoid hemorrhage. The patient was an immature, excessively dependent individual. He had been divorced a month before the subarachnoid hemorrhage. Thereafter, he felt "quite cheap and embarrassed." It was a crushing experience because he had never anticipated that it would happen, even though he had been separated from his wife for the previous two years. The divorce was on his mind, and he was getting more and more irritable before the subarachnoid hemorrhage. After the hemorrhage there were regressive changes in his personality, such as hypochondriasis, general irritability and the facial pain. These were benefited by psychotherapy (by Dr. Robert Seidenberg).

Spontaneous Subdural Hematoma

Case 12. A 48 year old woman had had generalized headache for three weeks without history of head injury. For the three days before admission the headaches had become more severe, and a left oculomotor palsy developed. *Examination* revealed that the patient was somnolent and had complete left oculomotor palsy. *Angiography* revealed a large subdural hematoma and localized variability in caliber of the ascending portion of the anterior cerebral artery in successive angiograms. The hematoma was evacuated surgically and recovery was uneventful.

Pertinent personal history revealed long-standing problems and anxiety. She had had unilateral frontal headaches at the time of her menses, and was childless. Menopause had occurred seven years previously. She tended to compete with her husband and had excessive fears concerning his injuring his fingers. For some time before the onset of the present illness she had not been sleeping with him. Her personal difficulties had been increasing until the present illness.

Hemorrhage into a Benign Intracranial Mass

Case 13. A 43 year old woman had had severe headache, vomiting, anorexia and drowsiness for three days before admission. In the past two days there had been complete loss of vision of the right eye. *Examination* revealed nuchal rigidity,

drowsiness and loss of light perception in the right eye. There was also loss of the temporal half of the visual field of the left eye. *Plain radiographs* and *angiograms* revealed an avascular intrasellar and suprasellar mass. The arteriograms showed variations in caliber of the horizontal portions of the anterior cerebral arteries, which were stretched over the mass. But these films were excluded from the study of spasm. Spontaneous recovery took place promptly, and six weeks later the visual acuity was normal in each eye. The left visual field was normal but the nasal half of the right field was still absent.

Pertinent personal history was obtained two months after the acute episode. Throughout her life the patient had been unable to express anger. A week before onset of present illness she had begun to have trouble with a querulous customer, who returned daily. She felt increasing anger but could not express it except to cry a little bit. Each day that she saw the irritating man she became more annoyed.

CASES OF SUDDEN HEMIPARESIS

Probable Thrombosis of the Internal Carotid at Its Origin

Case 14. A 69 year old woman, riding in a car one afternoon with her husband, slumped forward and became faint. Her systolic blood pressure was found to be 240, but she had no objective neurologic signs. A few hours later aphasia and right hemiplegia appeared. Some days later the pulsation of the entire cervical part of the right carotid artery and of the lower two thirds of the left carotid was normal. There was greatly diminished pulsation over the left carotid artery in the upper third of the neck. It was considered that the patient was probably suffering from thrombosis of the left internal carotid artery at its origin. Patient was not admitted to hospital, and no special studies were made.

Pertinent family and personal history: Patient's mother and sister had died of cerebral strokes at the ages of 65 and 60, respectively. The patient's systolic blood pressure had ranged between 165 and 200 for 10 years. One week before her stroke one of her best friends had died suddenly. The patient was greatly disturbed by the death and funeral of her friend.

Case 15. A 57 year old man awoke one morning unable to speak. Examination by his personal physician revealed right hemiparesis, including the face. *Examination:* There were complete motor aphasia, right hemiplegia and a moderate apraxia. An *electroencephalogram* showed slow waves localized over the left parietotemporal region. Spinal fluid was normal. *Cerebral angiography* was performed by injecting the left common carotid artery. Arteriograms made at the conclusion of injection showed good visibility of the branches of the external carotid artery but none of the internal. In attempted venograms made five seconds after injection the subarachnoid course of the internal carotid artery filled. This filling, through collateral vessels of the orbit, is characteristic of thrombosis (or at least physiologic obstruction) of the internal carotid artery in the neck. The films were not suitable for study of arterial spasm.

Pertinent personal history: A few years previously this man had had an important position with his company. He then suffered a series of demotions, which he ascribed to discrimination on the part of a new immediate superior. He developed hypertension which was present only when the company doctor examined him, and not at home. A week before his stroke he had been examined by the company doctor and his systolic blood pressure had exceeded 200. For this reason he was released from his job. His rage against the company reached a climax just before his stroke.

Hemiplegia without Evidence of Arterial Thrombosis

Case 16. A 41 year old man suddenly experienced right hemiplegia and aphasia. Within a few days there was complete recovery of the limbs, but speech remained

slow. Neurologic examination was otherwise normal. *Angiographic examination* revealed intermittent filling of each internal carotid artery, especially the left.^{1, figure 5} It was considered that this indicated intermittent spastic occlusion of both right and left internal carotid arteries. But this occlusion on the right side was asymptomatic.

Pertinent personal history: This patient seemed anxious and dependent. He had always been compulsive; for instance, at bedtime he checked the lights, gas, water and doors of the house several times. He had consulted a psychiatrist in the past because of excessive "worrying about everything." There is a family history of mental illness. For two years before the present illness the patient had had abdominal pain and frontal headaches following emotional stress at work.

A new product was being made by his department of the factory during the three or four months before the present illness. For one month before the stroke a time-study man had been sitting next to him watching him work in order to set up a standard pay schedule. The patient is an unusually fast worker. Therefore, if the time-study man established a rate based on his normal speed the other workers would suffer a drop in income; on the other hand, if he worked unusually slowly his conscience would bother him. This conflict was getting worse with each day of work. He was having more and more trouble sleeping, and the problem was always on his mind the few days before the stroke. The patient felt "wonderful" when in the hospital, but nervous and tense when he went home.

Comment: Knowledge of the pertinent personal history was of immediate practical value in this case, when the patient asked if he could return to work. The physician could then state, "Yes, if the time-study man is no longer at your bench."

Case 17. A 33 year old woman suffered sudden right hemiplegia and aphasia one morning. There were transitory fever and vomiting. Two days later the patient became more somnolent. *Angiography* was carried out 13 days after the stroke. These films revealed marked narrowing of the left internal carotid artery, both in the neck and intracranially. There was no filling of the middle or anterior cerebral arteries. The use of the patient's limbs improved, but aphasia persisted in moderate degree. Sixteen months after the original episode angiography was repeated. This time there was less severe narrowing of the internal carotid artery, and both the middle and anterior cerebral arteries were visualized.^{2, figure 2}

Pertinent personal history: As a child this patient had been considered a tomboy. She had been devoted to her father, with whom she spent a great deal of time. She had married a very quiet man. Two months before her stroke, her third child was placed in a plaster cast because of dislocation of the hip. At this time her headaches began. A week before the stroke her father suffered partial intestinal obstruction and was critically ill for two or three days.

Case 18. A 44 year old woman experienced heaviness of the feet one evening. By the next morning there was severe left hemiplegia. Since then she had been unable to dress herself and was mentally depressed. She feared that people would pity her, and had difficulty accepting help. *Examination:* Residual left hemiparesis, but the patient could walk with the use of a cane. The carotid pulsations and blood pressure were normal. No special examination was made.

Pertinent personal history: In earlier years this woman had been very vigorous and independent. She had been a registered nurse and had earned the money which allowed her husband to go through school. In recent years her husband had become less dependent on her, a situation hard for her to accept. She had suffered from dysmenorrhea associated with emotional depression for a number of years.

Case 19. A 17 year old boy, beginning to work with his father, suddenly suffered severe headache, right hemiparesis and aphasia. The spinal fluid was normal except for increase in protein content. Neurologic examination and pneumoencephalogram were normal. *Carotid angiography* revealed temporary blockage (attributed

to spasm) of the internal carotid artery. The patient suddenly became negativistic and mute. The next group of arteriograms, made a few minutes later, showed normal filling of the intracranial arteries. During a psychiatric interview a few weeks later, in the presence of his father, the patient suffered transitory aphasia.

Pertinent personal history: The patient was extremely shy, passive and somewhat effeminate. His father, who had been a successful athlete and is a vigorous, hard-working man, was intolerant of the patient's lack of vigor. The patient was generally fearful and inhibited. Additional details have been given elsewhere.^{1, case 6}

Case 20. A 36 year old woman, pregnant for the twelfth time and now approaching term, was admitted to the hospital with the chief complaint of right hemiparesis. Examination revealed mild right hemiparesis, marked by weakness, spasticity and increased tendon reflexes in the right limbs. The plantar response was equivocal on the right but normal on the left. The skin on the neck became red in patches when she was emotional. The spinal fluid was under normal pressure and had normal protein content. Angiography was not carried out.

Pertinent personal history: This patient had married at the age of 19 and had become pregnant 12 times in the subsequent 17 years. The last four or five pregnancies had occurred despite her best attempts at contraception. At the time of the last previous pregnancy she had wanted to ask the doctors to sterilize her but was unable to bring herself to do so. She burst into tears when discussing these matters. Four months before the onset of the present illness there had been transitory numbness of the right limbs, which cleared in an hour or two. The present episode of hemiplegia began with aphasia. For these reasons, the doctors spontaneously suggested tubal ligation to follow the pregnancy.

DISCUSSION

Personality and Life Situation: In the cases where psychiatric consultation was carried out it was found¹ that these people have great difficulty in dealing with aggressive and hostile feelings. Engel and colleagues² also found that, in male patients with hemiplegia and migraine, anger was the dominant emotion, either unexpressed or expressed with feelings of guilt. The women of our group tended to disdain their femininity and tried to compete with men.¹

There were 13 cases in which significant character structure was found, and 15 with an apparently precipitating emotional stress. In eight cases both factors were found. If psychiatric consultation had been available in all cases these figures would undoubtedly have been higher.

Angiographic Demonstration of Arterial Spasm: My colleagues and I have previously demonstrated angiographically the presence of spasm of the major cerebral arteries,^{1, 2} and have discussed the reliability of our interpretation.² We have found such spasm in 90 per cent of the patients with cerebral stroke. On the contrary, in the general run of patients requiring angiography, such as brain tumor suspects, spasm is demonstrable in about 10 per cent of the cases. Therefore, we believe that in the patients with stroke, at least the threshold for the production of spasm is lower than average.

Angiograms were made in 17 cases of the present series of cases. In 15 of these the films were technically suitable for study of spasm (i.e., at

least two different arteriograms in the same projection). In all 15 there was strong evidence of arterial spasm.³

Physiopathologic Aspects: In 1945 Aring⁴ reviewed the pertinent literature and concluded that cerebral vascular disorders often result from dynamic changes in the cerebral blood vessels. I believe that emotional stress (perhaps by liberating vasopressor substances into the blood stream) induces such contraction of the cerebral arteries. The result of excessive spasm of cerebral arteries causes ischemia. The cerebral and vascular effects of ischemic anoxia depend on the exact location, severity, linear extent and duration of the contraction, as well as on the collateral circulation and the systemic blood pressure. Ischemic effects on cerebral tissue include cerebral edema, necrosis, hemorrhage, demyelination, cyst formation and gliosis. The result of anoxia on capillaries includes increased permeability to fluid, then to protein, and finally to red blood cells. The ischemic effects on the walls of the arteries may result in local edema (as in migraine), atrophy, necrosis with hemorrhage, thrombosis or perhaps even aneurysmal formation and rupture.

SUMMARY

Twenty patients with cerebral vascular disorders have been presented. Most were under the age of 50. In 13 cases there was nontraumatic intracranial hemorrhage, and in eight cases hemiparesis that was clearly organic; one patient (case 3) had both subarachnoid hemorrhage and hemiparesis. In 13 of these cases there were long-standing personality difficulties preceding the stroke, and in 15 a special emotional stress which immediately preceded the stroke; in eight cases both factors were present.

Angiograms technically suitable for study of spasm of the cerebral arteries were available in 15 cases. In all of these there was an excessive tendency to arterial contraction. This spastic tendency may be one of the bodily expressions of the emotional disturbance. Ischemia resulting from excessive arterial contraction doubtless contributes to the pathologic changes in the brain and its blood vessels. Be that as it may, the high incidence of major emotional problems preceding cerebral strokes warrants further attention.

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ON THE DIAGNOSIS OF MALIGNANT LYMPHOMA OF THE GASTROINTESTINAL TRACT *

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MALIGNANT lymphomas whose primary manifestations are in the gastrointestinal tract have aroused our interest because of their unusually high incidence among patients operated upon at the Presbyterian Hospital in recent years, an incidence well beyond that reported from institutions of greater size. During the five year period 1947-51 selected for our study, these tumors comprised 20 per cent of malignant tumors of the *stomach* found at operation (national average, 2 to 3 per cent), and virtually half of those removed from the *small intestine*. As one would expect, they represent a very small percentage of malignant tumors encountered in the large bowel.

A prime function of this study, then, is to emphasize the necessity for including lymphoma *regularly* in one's critical appraisal of gastrointestinal lesions, a duty which falls chiefly to the internist and radiologist. We will also point out the few aids in diagnosis that have become apparent in our survey and those of other authors, with the full realization that they are still inadequate for precise identification of the tumor. We wonder how often a large malignant tumor of the stomach is dismissed as completely inoperable, and how often, even in those patients whose abdomen is explored, only a large lymph node is removed and the enlargement found later to be inflammatory. At least some of these patients must surely have lymphomas amenable to x-ray or chemotherapy, and thus could be restored to relative good health for significantly long periods of time. The hope for salvage of this sort stands foremost among our reasons for submitting this report.

Many of the articles dealing with this subject are difficult to evaluate because of the tendency to divide the tumors according to their histologic pattern. For example, one author will be concerned with Hodgkin's disease of the stomach, another with lymphosarcoma, still another with reticulum cell sarcoma, and so on. We believe that the problem can be more clearly faced by regarding the entire group as a single neoplastic entity under the heading of malignant lymphoma, to include the following types: follicular, lymphocytic, reticulum cell and Hodgkin's. As outlined by Jackson and Parker,¹ Hodgkin's lymphoma is divisible into three subgroups: paraganuloma, granuloma and sarcoma. For the most part, however, the various

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individual members of this family behave in much the same fashion clinically. Furthermore, the histologic pattern of a given tumor is anything but static. Custer and Bernhard² and Custer³ have shown that a significantly high percentage of lymphomas undergo a complete change in their cellular structure, as indicated by figure 1. If one takes the trouble to perform serial biopsies throughout the course of a malignant lymphoma, one or more transitions in the histologic picture will often be revealed and the whole will develop as a series of scenes of a single drama. Very frequently two or more histologic types coexist in the same patient, even in the same tumor mass. An alertness toward sensing a change in type or a transformation from a

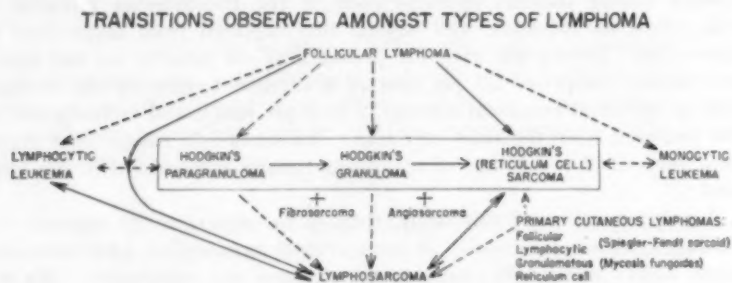


Fig. 1. Diagram of observed transitions between the various lymphoma types.

local to a systemic form of the disease is valuable from the standpoint of clinical management, as is the realization that one is treating the same general illness, no matter what its complexion.

SYMPTOMS AND SIGNS

Most attempts in the past to diagnose malignant lymphoma of the digestive tract prior to biopsy or resection have met with failure when reliance was on only *one* method of diagnosis. Like other diseases, this one must be approached from *every* diagnostic angle if any degree of success is to be achieved. Inspection of the clinical evidence will serve to determine how valuable it may be. Table 1 shows the symptoms noted in 22 cases of lymphoma, 15 of stomach, five of small bowel and two of colon.

In the gastric lesions, epigastric pain of some type is stressed as the most important symptom in all series (a recent review recording it in 84 per cent).^{4, 5, 6, 7, 8} There was epigastric pain in 11 of our 15 cases, some of the ulcer type, but more usually atypical. Three had none. The small and large bowel tumors showed a predominance of midabdominal or lower abdominal pain.^{4, 5, 8}

Hematemesis or melena is not usual or frequent among previously reported cases, and appeared in only four of our 15 stomach tumors, none of the intestinal lesions having bled.

A normal leukocyte count is found in almost all patients not having leukemia. However, the erythrocyte level is of special interest in differentiating these lesions from carcinoma. Most authors ^{4,6} agree that in lymphoma anemia is uncommon, even rare; if present, it is very slight. Our findings coincide. Six of our stomach and only one of the bowel cases revealed slightly depressed red cell counts and hemoglobin values. (One

TABLE I
Gastrointestinal Lymphoma—Symptoms and Signs in 22 Cases of This Report

	Stom.	S. B.	Colon
Cases—	15	5	2
Pain: Epigastric:	11	1	0
Constant, no relation to food	3	0	0
Constant, relieved by food	2	0	0
Constant, aggravated by food	3	0	0
Intermittent	1	1	0
On palpation only	2	0	0
Mid or lower abdominal:	0	3	2
Constant	0	1	0
Intermittent	0	2	2
None	3	0	0
Not recorded	1	1	0
Loss of Blood:			
Hematemesis	2	0	0
Melena	2	0	0
Anemia:			
None	8	3	2
Slight	6	1	0
Marked	0	0	0
Not recorded	1	1	0
Anorexia:	13	4	0
Nausea:	8	2	0
Vomiting:	8	4	0
Palpable Mass:			
None	7	3	1
Present	7	1	1
Not recorded	1	1	0
Loss in Weight:			
None	3	0	0
Average in others (lb./mo.)	5	4	4.5
Maximum (lb./mo.)	16	4.5	7.5
Not recorded	1	3	0
Range	0-43		
Average	14		

might note the same in a group of supposed normals.) This contrasts sharply with the findings in carcinoma.

Anorexia is common in gastrointestinal lymphoma,^{4,6} occurring with 13 of our 15 stomach tumors and in four of the five small bowel tumors. Nausea and/or vomiting appears in 25 to 50 per cent of patients with tumors in the stomach, and in about 60 per cent of those with small bowel lesions.^{4,6,8,9}

Gastric acidity has not been investigated in the present series, but others^{4, 6, 9, 10, 11, 12} quote 50 to 80 per cent of stomach lesions accompanied by hypochlorhydria or achlorhydria. This would seem to be a valuable aid in differentiating ulcerated lymphomas from peptic ulcers, but reliance on a normal acid curve is no safer than when dealing with carcinoma of the stomach.

A palpable mass occurred in 15 to 35 per cent of reported stomach cases^{6, 8, 13, 14} and in 50 per cent of ours. In the bowel tumors it occurred in 38 to 86 per cent^{8, 15, 16}; in ours, in about 28 per cent.

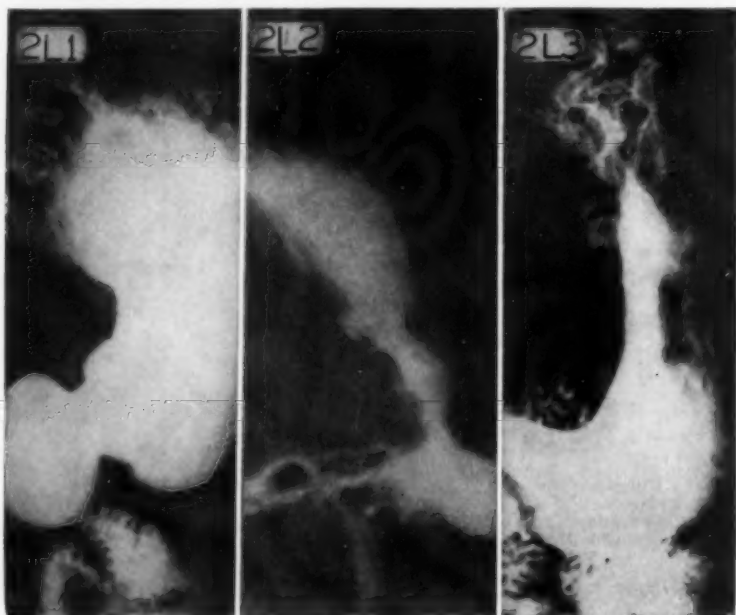


FIG. 2A. Lymphoma of the stomach ulcerating the lesser curvature (three cases). Note similarity to figure 2B (2G1).

Weight loss is a frequent sign of stomach lymphoma, being noted in 60 to 95 per cent^{4, 6, 8} (ours, 73 per cent). Total weight loss in our cases ranged from 0 to 43 pounds, averaging 14 pounds. There is general agreement, however, that this is not so marked as in carcinoma. This may be demonstrated with great clarity by comparing the moderate weight loss to the oftentimes huge lymphomas visualized in roentgen studies. Thus, in any individual case one cannot rely on loss of weight to initiate suspicion, since some lesions will have reached great size before causing this sign. In small bowel and colon disease, records of weight changes are insufficient to be useful.

Loss of energy of slight to moderate grade was usual in the entire group, but it is not a specific sign.

As to small intestinal lesions, Portmann's recent review of the literature⁴ shows that several types of clinical picture may be encountered: (1) obstruction, usually partial and chronic, the most common; (2) the enteritis type; (3) peritonitis with perforation, and (4) rarely, right lower quadrant

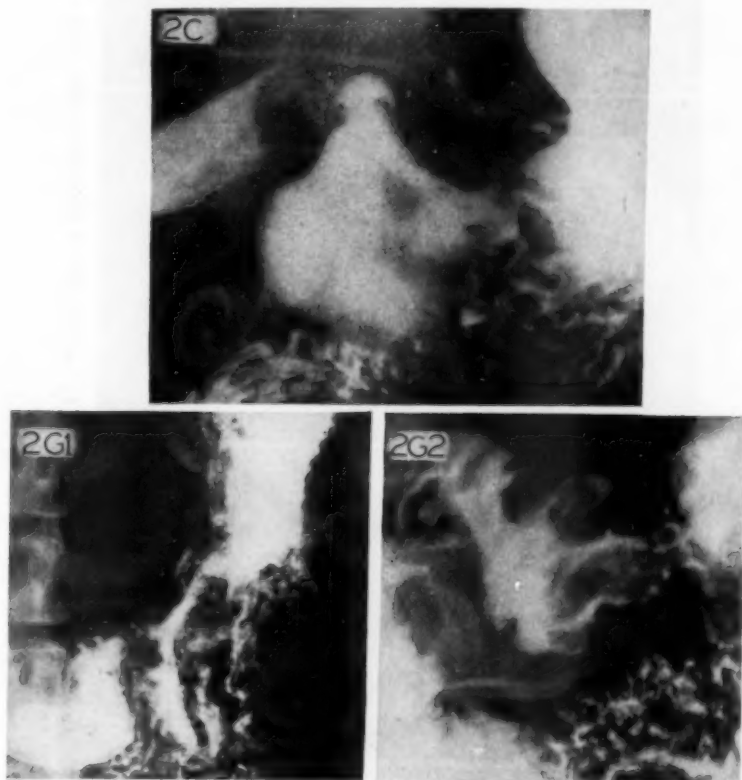


FIG. 2B. Above (2C): Carcinoma ulcerating the lesser curvature. Below (2G1): Gastritis with ulcer of lesser curvature; (2G2): Gastritis of antrum in an ulcer patient.

pain and tenderness suggesting appendicitis. Our experience, mostly in generalized lymphoma, is with the so-called enteritis picture: low grade fever, anorexia, vague "indigestion" or localized abdominal pain, loss of energy, perhaps diarrhea or unaccustomed constipation, and slight weight loss. We have seen only three cases of perforation, none occurring in the

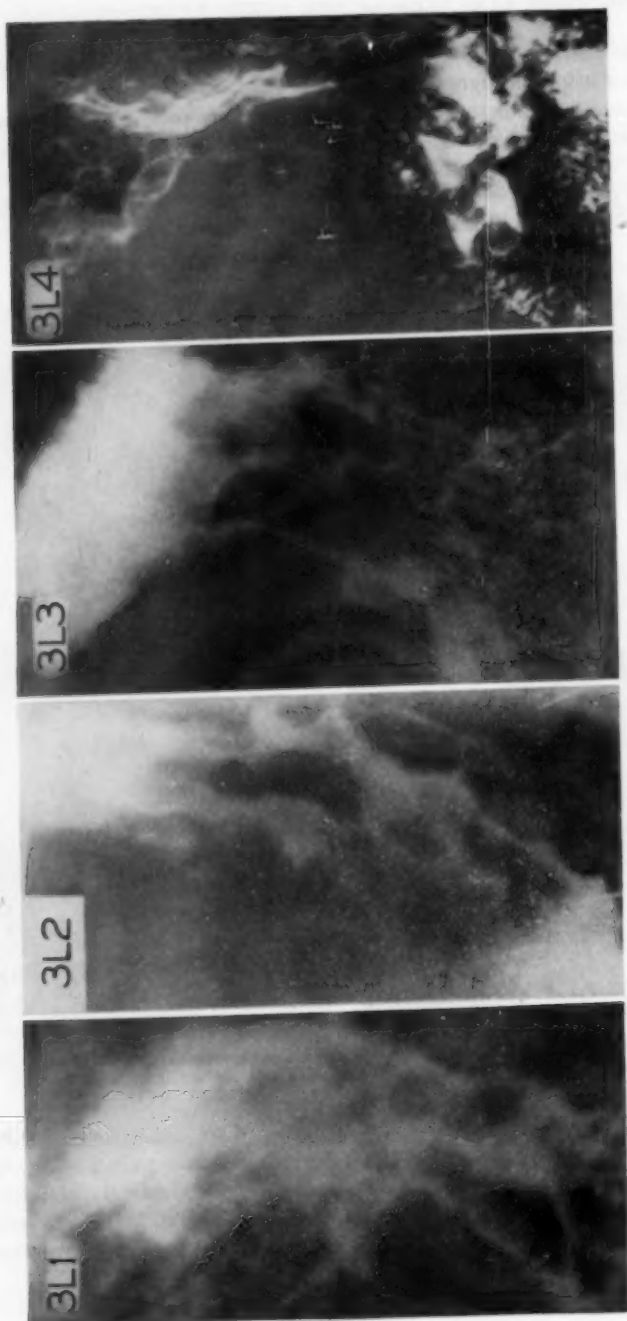


FIG. 3A. Lymphoma infiltrating the stomach (four cases shown here and the fifth in figure 3B). Note large irregular rugae.

five year period included in this report. Remitting high fever seems to occur mostly with extensive associated involvement of lymph nodes.

Malignant tumors of the small bowel are not common, and may appear radiologically as regional enteritis²; but, as the records accumulate, it is our impression that malignant lymphoma will show an increasing frequency

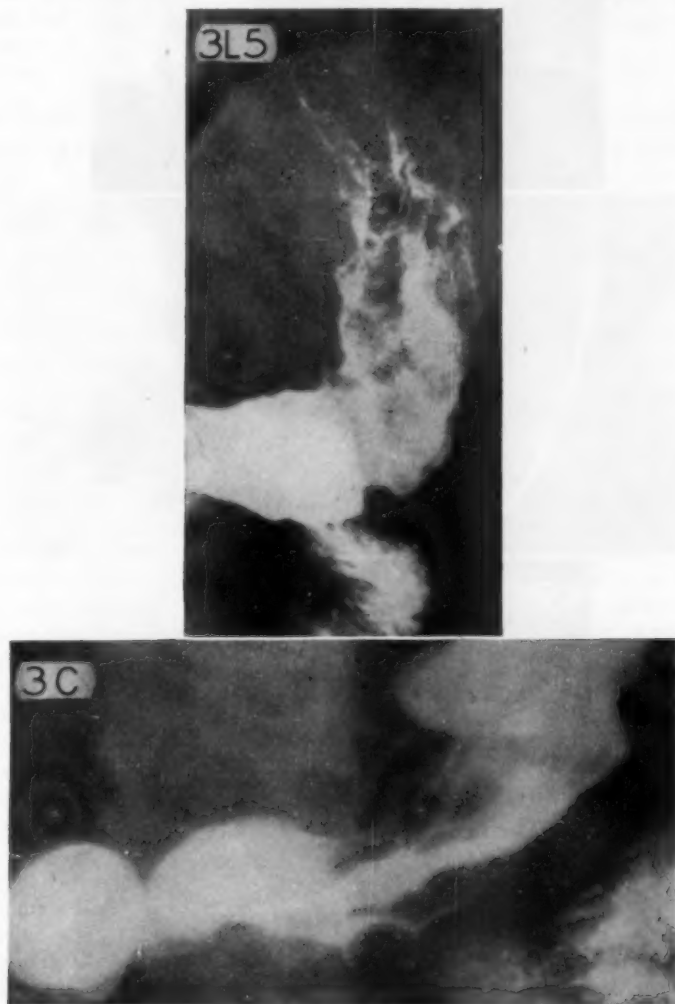


FIG. 3B. *Above:* Continuation of figure 3A. *Below:* Carcinoma infiltrating body of stomach.

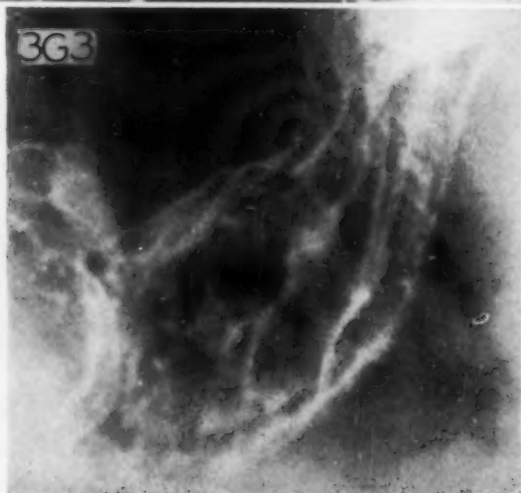
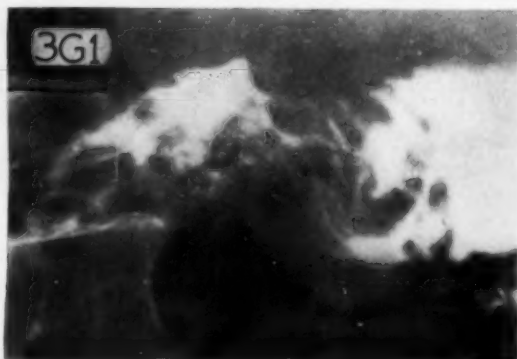


FIG. 3C. Gastritis of infiltrative type (three cases).

relative to carcinoma. Our ratio of operated cases is lymphoma five to carcinoma six (extremely high).

Lymphoma of the colon is very rare in any series^{4, 15, 17, 18} and is hardly to be differentiated from carcinoma, unless it is widely invasive. We have had only three, and correctly diagnosed two. The symptoms are those one expects in connection with obstruction or infiltration: pain, palpable mass, weight loss, change in bowel function, and possibly acute or chronic peritonitis.

ROENTGENOLOGIC STUDIES

1. *Stomach:* Roentgen examination of the stomach is of primary aid in locating the source of trouble, and is usually successful in labeling it as malignant. Alone, it is seldom sufficient to differentiate the tumor from carcinoma. In 1926, Holmes et al.¹⁹ wrote: "The roentgen findings are not sufficiently characteristic to permit of a specific diagnosis of lymphoblastoma of the stomach, but, when taken with clinical findings, may be of considerable value." Nearly all other authors agree.^{6, 12, 20} The usual roentgen diagnosis is carcinoma or benign peptic ulcer. A recent test with our own teaching collection of roentgenograms from cases of carcinoma and lymphoma, excluding all clinical information, demonstrated low accuracy when only the roentgen data were used for evaluation. Most of the lymphomas in this report can be imitated closely by the carcinomas in our roentgenographic files of proved cases.

The third lesion causing serious difficulty in roentgen diagnosis is hypertrophic gastritis (with or without ulcer). Even with all the clinical data available, the preoperative and operative diagnosis may be very difficult.

The types of configuration of lymphoma of the stomach vary widely. We cannot agree with those describing large lobular or whorl patterns, or large rugae, as valuable aids in differential estimate.¹⁵ By means of juxtaposition of illustrations, we can show lymphoma, carcinoma and gastritis to present a similar appearance in roentgenograms (figures 2 to 5).

Figures 2 A and B show three ulcerated lymphomas, one ulcerated carcinoma and two cases of benign ulcer accompanied by gastritis. Repeated study of the mucosa may disclose strong suggestions of malignant quality in some such lesions, but the task is very difficult on the whole.

Figures 3 A, B and C display examples of infiltrating disease in the three categories. This group is perhaps the most confusing of all, because the large, irregular or tortuous rugae, or even the flattening of mucosa, may be produced by either inflammatory or neoplastic tissue.

Figures 4 A and B exemplify the polypoid architecture, of which we have none in gastritis.

Figures 5 A, B and C are of the fixed constrictive group. The pyloric and antral lesions (the numbers 1) are among the most interesting, all so classically carcinoma.

An inspection of this material will explain the need for repeated roentgen

examination in this type of gastric disease. Just as one permits physical findings and laboratory material to be restudied and confirmed, so must it be appreciated that a single roentgen observation, even in competent hands, may not be reliable.

The large and angry lesions shown radiologically may profitably be compared with the clinical state. All available data should be reviewed before making a radiologic diagnosis. Although chronic gastritis will create a similar and confusing complex, a strong suspicion of malignant lymphoma should arise when there exists the combination of pain, atypical or typical of

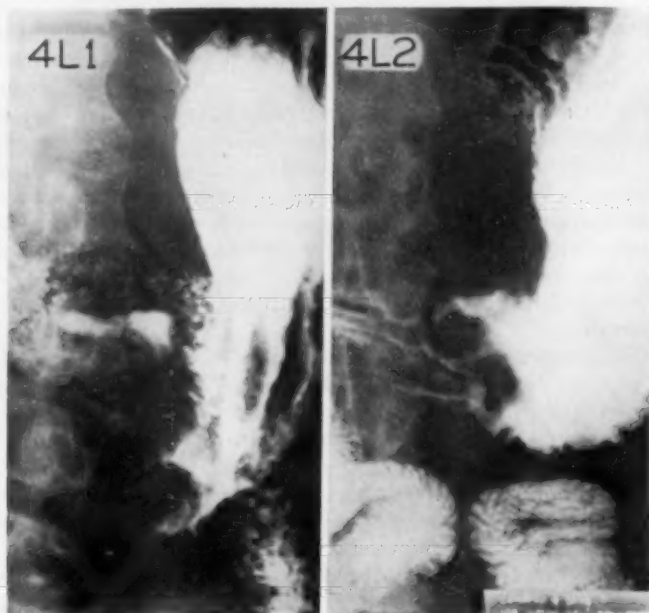


FIG. 4A. Lymphoma of distal portion of stomach of polypoid nature (two cases).

ulcer, slight or no anemia, anorexia, slight to moderate weight loss, decreased or normal gastric acid, and roentgen evidence of a lesion usually large and often involving two thirds to three quarters of the stomach. Our diagnostic score on roentgen examination, as seen in table 2, is not too poor, but it will be better in the future if we insist on complete clinical and laboratory data before attempting a differential diagnosis. Too often the barium examination is the first performed; too often it is expected to produce an infallible and immediate answer, even before the films are dry. It must be appreciated by the radiologist and the clinician that the history, physical signs and

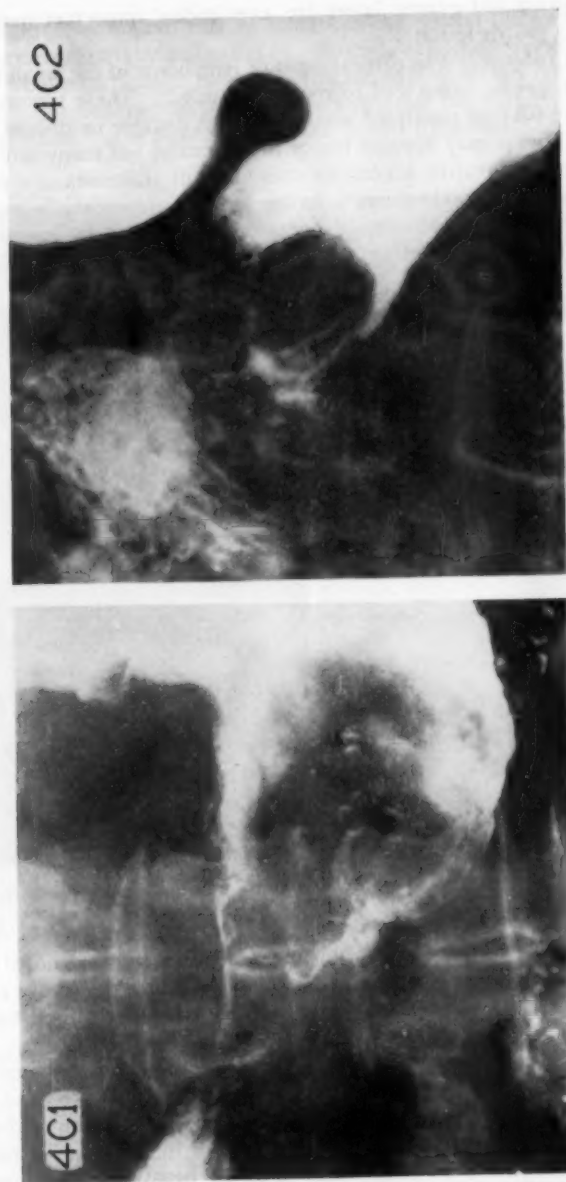


FIG. 4B. Carcinoma of distal portion of stomach of polypoid nature (two cases).

analysis of blood and gastric juices are, even today, important items in the appraisal of a gastric lesion.

2. *Small Intestine*: The clinical signs of lymphoma of the small intestine, although nonspecific, often lead to roentgen study.²¹ These tumors may be single (figure 6A) or multiple,⁵ small or large,⁹ discrete or diffuse (figures 6B and 7). Some may suggest tumor immediately, but many will disclose a nondescript, infiltrative lesion, as one finds in inflammatory enteritis.⁴ Others, especially secondary ones, have appeared to us like a nonspecific motor disturbance with changeable dysfunction, which can be confused with a nutritional disease or other diffuse peritoneal irritation.¹⁷ Especially

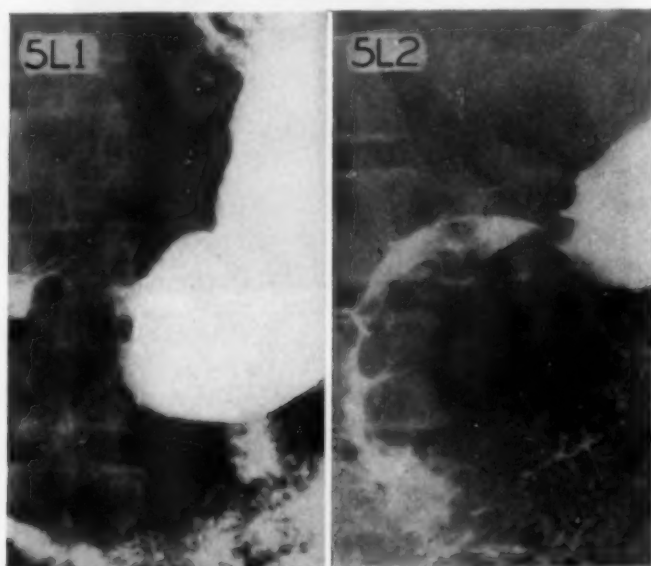


FIG. 5A. Lymphoma of antrum and pylorus of constrictive type (two cases). On the right, involvement of duodenum.

elusive are the bowel lesions created by adherent lymphomatous nodal masses (figure 6A showing one of those more usually found). Physical examination has been an invaluable aid to us in this last type, often disclosing such enlargements.

3. *Colon*: The total experience of any one author with lymphoma of the colon is very small.^{4, 8, 9, 15, 18} Most occur in the cecum or rectum. The latter must be clearly differentiated from the non-neoplastic lymphoid polyps. There are only three lymphomas in our series (none in the cecum or rectum). One (figure 8A) is a large mass localized at the hepatic flexure, appearing just as a carcinoma. Two others (figure 8B) are quite different, being

diffuse, infiltrative, nonobstructive lesions. The second plate in figure 8B is from the case illustrated in figures 5L, 6B and 7, the most extensive gastrointestinal lymphoma known to us, the patient having shown but few manifestations. We believe the local obstructive type not differentiable from carcinoma. For the diffuse variety, the initial diagnosis should be lymphoma.

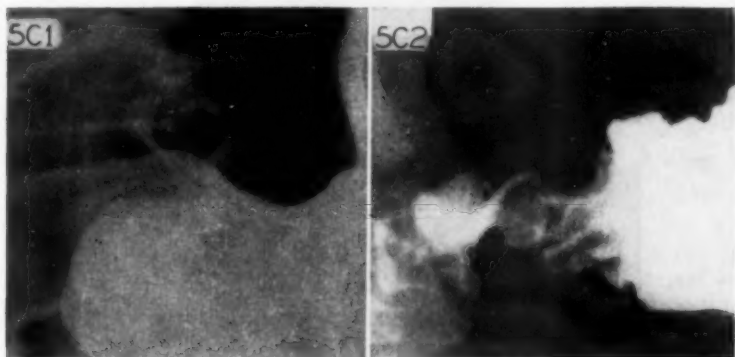


FIG. 5B. Carcinoma of antrum and pylorus, constricting (two cases).

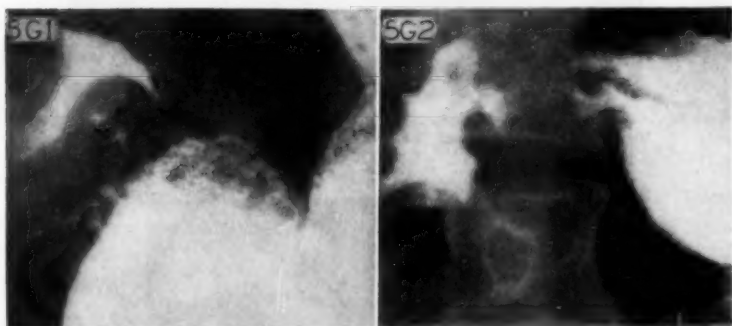


FIG. 5C. Gastritis of antrum and pylorus, constricting (two cases).

OTHER DIAGNOSTIC AIDS

Gastroscopy has been of little aid in arriving at a final decision. Spencer and others¹⁴ recognized two of 15 cases. In Crile's series,⁶ one of 19 was correctly diagnosed, although a neoplasm was described in all.

The gross operative diagnosis per se, like the radiologic or gastroscopic, is unreliable. The location and extent of a gastric lymphoma often mimic those of carcinoma. The presence of enlarged neighboring nodes adds nothing to the differential features. A tabulation of the data in past reports

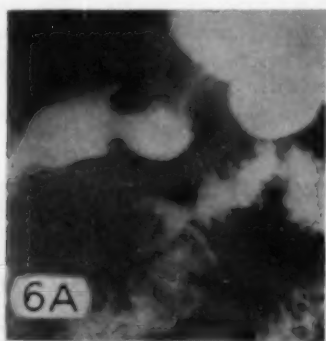


FIG. 6. *A*: Lymphoma of duodenum, focal. *B*: Lymphoma of duodenum and jejunum, diffuse. Same case as figure 5L1.



FIG. 7. Lymphoma of terminal ileum. Same as figures 5L1 and 6B.

TABLE II

Patient	Gastric Lymphoma Roentgen Features in 10 Cases of This Report						X-ray Diagnosis
	Location	Extent	Ulcer	Infl.	Polyp.	Const.	
My.	Distal $\frac{1}{2}$	+++	+	+++	+		Lymphoma sec.
Sm.	Distal $\frac{1}{2}$	+++	+	+++	++		(Not our diag.)
Sa.	Lesser Curv.	++	+	++			Benign Ulcer
Pl.	Mid. $\frac{1}{2}$	+++	+	+++	+		Ca. or lymphoma
Ha.	Distal $\frac{1}{2}$	+		+	++		(Not our diag.)
Mc.	Distal $\frac{1}{2}$	+++		+++	+++		Probably Ca.—Sa?
St.	Prox. $\frac{1}{2}$	+++		+++			Ca.
Ni.	Distal $\frac{1}{2}$	+		+		++	(Not our diag.)
Fa.	Lesser C. + Antrum	+++		+	+		Ca. or Sa.
Na.	Distal $\frac{1}{2}$ + Duod.	++		++	+	+	Lymphoma sec.

on regional nodes found histologically to contain tumor may be seen in table 3.^{6, 9, 12, 18, 21, 22}

Frozen section examination of nodes near a lymphoma may reveal no tumor, since many will be purely reactive, and the tumor will remain unidentified. A piece of the primary tumor itself given to the pathologist affords greater accuracy, but, even then, paraffin sections are generally required for definitive diagnosis. Reticulum cell sarcoma, for example, may be impossible to differentiate from anaplastic carcinoma. Thus, two final points can be emphasized: (1) that large, unresectable tumors of the stomach or intestine may *not* be carcinoma and, therefore, hopeless; (2) that the surgeon should biopsy each primary tumor (not merely a lymph node), in the hope that it may prove to be a lymphoma and thus be responsive to irradiation and/or chemotherapy.

SUMMARY

1. During a five year period in a medium-sized general hospital an exceptionally large number of malignant lymphomas were identified in operative specimens from the gastrointestinal tract, representing 20 per cent of all malignant tumors removed from the stomach and nearly half of those

TABLE III
Occurrence of Regional Nodes Histologically Positive for Various
Gastrointestinal Lymphomas*

Stomach	Small Bowel	Colon	All Intestine	Entire G.I. Tract
24%	0%		68%	12%
29	60			60
25				18
				21
				38
Avg. 26%	30%		68%	30%

* Each figure denotes a report in the literature.

from the small intestine. Lymphomas of the colon were numerically and proportionately low in incidence.

2. Preoperative diagnosis of gastrointestinal lymphoma is difficult and requires careful correlation of clinical, radiologic and laboratory data to be successful in a reasonable proportion of cases. For example, the combination of epigastric pain, anorexia, nausea and vomiting, without signs of obstruction, slight to moderate weight loss, presence of a palpable mass, little or no anemia, and roentgen evidence of a large and angry looking tumor of the stomach, should lead to a strong suspicion of gastric lymphoma. Roentgen study alone is mostly unsuccessful in the differential diagnosis;

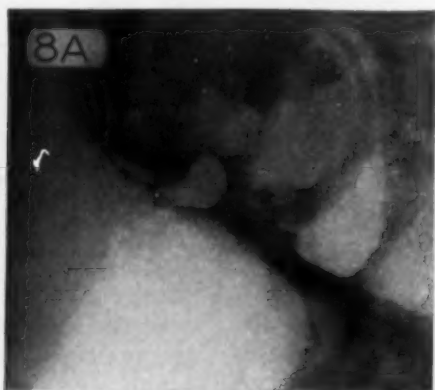


FIG. 8A. Lymphoma of hepatic flexure of colon, localized, polypoid and obstructive. Compare with typical carcinoma.

roentgenograms are presented from lymphoma, carcinoma and chronic gastritis that are virtually interchangeable.

3. If the tumor found at operation is unresectable, the surgeon should remove a portion of the main mass for pathologic study, and not be content with biopsy of neighboring lymph nodes. Frozen section diagnosis of tumor tissue is unreliable.

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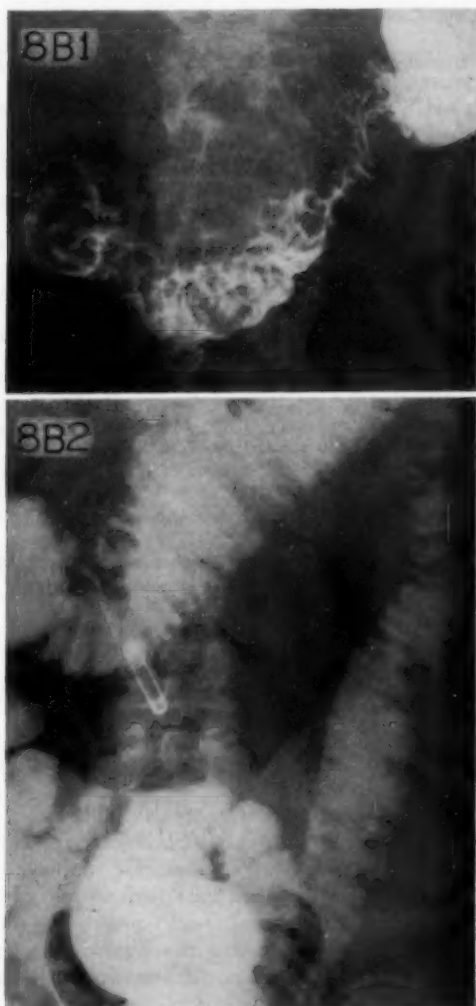


FIG. 8B. Lymphoma of colon, diffuse (two cases). Diagnosis of choice is lymphoma.
Figure 8B2 is same case as in figures 5L2, 6B and 7.

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MASSIVE DILATATION OF THE LEFT AURICLE: REPORT OF THREE CASES *

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THE occurrence of moderate dilatation of the left auricle in chronic rheumatic carditis and mitral valvulitis is a well known finding. However, extreme dilatation of either the left or the right auricular chamber is quite uncommon. Since the first clinical and pathologic description of enormous enlargement of the left auricle by Owen and Fenton in 1901,⁹ less than 50 cases have been reported to date. These reports refer either to a tremendous symmetrical enlargement or to "aneurysmal dilatation" of the left auricle. Except for the rare case of localized auricular aneurysm due to adjacent pulmonary or mediastinal disease, auricular arteritis or infarction, those cases reported can be grouped together as evidences of massive left auricular enlargement. The characteristics of the clinical picture of such enlargement have been repeatedly demonstrated and depend mainly on the pressure exerted on surrounding structures.^{7, 11, 17, 22, 24}

It is our contention that, although uncommon, such enlargement probably occurs much more frequently than the literature would indicate. Seemingly, each previous author interested in the subject was able to compile a number of similar cases once he became aware of the condition. Similarly, three cases were found by us within a period of several months. It is felt that a review of this condition is indicated so that a greater awareness of the clinical manifestations may preclude unnecessary operative procedures undertaken to determine the nature of a right sided thoracic mass which might be mistaken for a mediastinal or intrathoracic tumor. Furthermore, because the hugely dilated left auricle may also in rare instances resemble a right sided pleural effusion or pericardial effusion, unnecessary and hazardous diagnostic needling may be avoided if this entity is kept in mind.

Two cases are presented as examples of chronic rheumatic carditis with massive left auricular enlargement, and a third showing massive dilatation of both right and left auricles. No case similar to the latter has been reported to our knowledge.

CASE REPORTS

Case 1. A 26 year old female was first seen on February 18, 1952, with the chief complaint of mild dyspnea on exertion. The patient dated the onset of her present illness to November, 1951, at which time she had noted moderate shortness of breath on performing exercises that previously had never bothered her. About

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the same time she noted slight nocturnal edema of the ankles. She complained of occasional pain in the region of the left breast, sharp or throbbing and lasting only several seconds. She denied any orthopnea, paroxysmal nocturnal dyspnea, hemoptysis, cough or undue fatigue. There was no history of rheumatic fever, arthritis, scarlet fever or chorea. She stated that she had always been extremely active as a child, without any limitation in activity. There were no vague illnesses characterized by malaise, chills or fever. She did have rather frequent upper respiratory infections. Previous physical examinations apparently had not revealed any abnormalities. The patient's family and personal history was not relevant.

The physical examination revealed a short, well developed, well nourished young female in no distress. A slight malar flush was present. There was no venous distention. The trachea was midline. Chest examination revealed normal symmetry, with no superficial dilated veins. Respirations were 14 to the minute. There were greatly diminished breath sounds and vocal fremitus over the right lower third of the posterior chest wall, with dullness over this area. The blood pressure was 130/70 mm. of Hg in both arms. The pulse revealed auricular fibrillation, with a ventricular rate of 80 to 100. Examination of the heart showed the point of maximal impulse in the fifth interspace at the anterior axillary line. The area of cardiac dullness extended to both the right and left anterior axillary lines. With the patient supine there was no apparent shift in the dullness. No paradoxical pulse or friction rub was present. The aortic sounds were distant and no murmurs were audible at the base. The second pulmonary sound was accentuated, and a Grade II systolic murmur was heard in the left second interspace. Along the left sternal border in the third and fourth interspaces a blowing diastolic Grade II murmur was present. A diastolic thrill occurred at the apex, with Grade III systolic and diastolic murmurs. A systolic expansion of the right anterior chest wall was visible and palpable. The liver was palpable two fingerbreadths below the right costal margin and appeared slightly tender to palpation. There was no ascites, clubbing or edema.

Laboratory work showed a red blood cell count of 3.6 million; the hemoglobin was 13.5 gm. The white blood count was 7,500, with 57 per cent neutrophils and 39 per cent lymphocytes. The sedimentation rate was 1 mm. per hour. Total proteins were 6.2 mg. per cent; albumin, 3.9; globulin, 2.3. Fasting blood sugar was 99 mg. per cent. Thymol turbidity was 0.9 units; cholesterol, 117 mg. per cent. The cardiolipin was negative. Urinalysis was normal. An electrocardiogram revealed auricular fibrillation with occasional ventricular extrasystoles, right axis deviation, marked clockwise rotation and evidence of nonspecific myocardial damage. Little electrical activity was noted from leads taken over the right precordium.

Chest x-ray (figure 1) revealed extreme enlargement of the cardiac silhouette, the right cardiac border extending to within 1 cm. of the lateral rib cage. The left cardiac border was enlarged to a lesser degree, its inferior position extending to within 2 cm. of the rib cage. Cardiac fluoroscopy revealed marked enlargement of both ventricles and vague systolic pulsations of the right thoracic mass. The esophagus was displaced posteriorly and to the left, and was partially obstructed at the upper border of the left auricle. On the antero-posterior view, the barium-filled esophagus curved to the left. The left main stem bronchus appeared elevated and somewhat compressed. Irregular densities in the right lower lung field were interpreted as representing pressure atelectasis from an enlarged heart and/or a mediastinal mass.

Teleroentgenogram of the chest revealed the transverse diameter of the heart to measure 237 mm. Normal allowance for this patient's height and weight was 107 mm., showing 121 per cent enlargement of the transverse diameter of the heart. Cardiac catheterization revealed only moderate pulmonary artery hypertension of 62/20 after exercise and a diminished cardiac output of 3.65 L./min. There was no evidence of

intermixing of blood. Venous pressure was 6 cm. The circulation time was 20 seconds arm-to-tongue and 8 seconds arm-to-lung.

An angiocardiogram was done in an attempt to distinguish between the presence of massive auricular enlargement on the basis of rheumatic heart disease or an extracardiac mass in addition to the rheumatic heart. Six films were taken during a 15 second interval. The dye was seen to fill the right auricle, right ventricle and pulmonary artery, these structures being sharply displaced to the left by a large mass projecting from the right mediastinum. Subsequent films showed considerable delay in circulation, with dye remaining in the main pulmonary artery and its branches in the sixth film. No dye was seen to enter the mass itself.

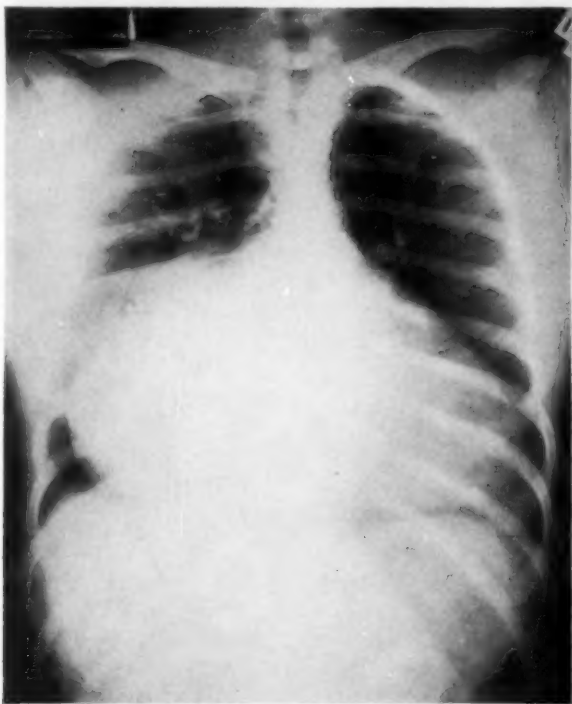


FIG. 1. *Case 1.* There is extreme enlargement of the heart shadow to the left and to the right. The left auricle extends almost to the right thoracic wall.

The patient was placed on anticoagulant therapy and then digitalis and quinidine in an attempt to convert the auricular fibrillation. Despite large doses of quinidine, this proved unsuccessful. Since the entire study, including the angiograms, led to no conclusive diagnosis, it was agreed that an exploratory thoracotomy should be done. Operation revealed a tremendously dilated left auricle with evidence of adjacent old pericarditis. There was no evidence of a mediastinal mass. The patient made an uneventful postoperative recovery and has since been maintained on digitalis therapy with relatively few symptoms.

Case 2. A white married female, age 31, was first seen in December, 1947, because of marked dyspnea.

Her birth and development had been normal and she was perfectly well until the age of 12, at which time she had fever and swollen ankles which were diagnosed as rheumatic fever. When she was 14 she had scarlet fever and was in bed for eight weeks, so it is probable that she had another episode of active rheumatic fever at that time. She subsequently felt well until the age of 18, when she developed constant fatigue and episodes of dyspnea. Her physician at that time kept her in bed for a year, after which she felt much better and was able to work as a waitress, with only

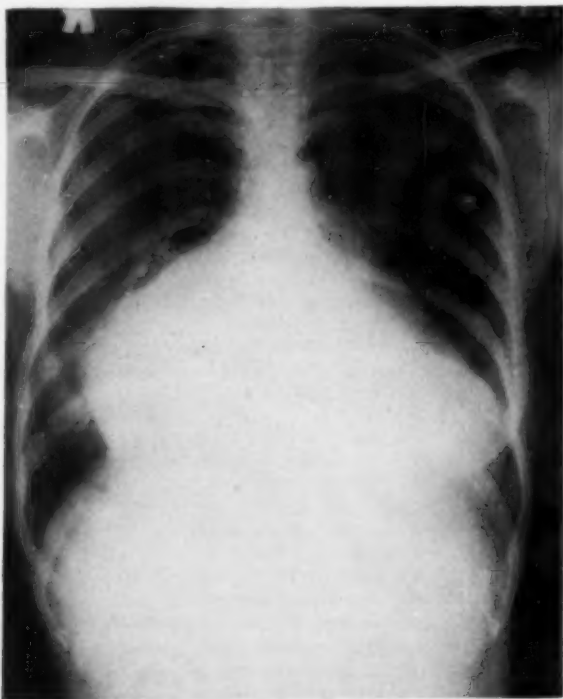


FIG. 2. *Case 2.* There is marked enlargement of the heart shadow in both directions. Note the greater density of the right heart shadow.

mild dyspnea, for the following three years. Thereafter she noted progressive shortness of breath, ankle edema, swelling of her hands and face, and some indefinite dysuria with dark-colored urine.

When she was 25 these symptoms caused her to see a doctor, who digitalized her for a "bad heart." She took digitalis most of the time after that. There were no apparent recurrent urinary symptoms. She married at 26 and continued to have episodes of nocturnal dyspnea and "tired spells," during which time she had a dry, hacking cough.

By the time she was 29 she often had to go to bed for periods up to two weeks at a time because of dyspnea, edema and orthopnea. She also had recurrent dull aching pains in her precordium, radiating straight through to her back which "seemed to cut off her breathing."

At the time she was first seen by one of us she was quite dyspneic and orthopneic, with no evidence of edema. She was so depressed she expressed the desire to die. System review, family history and social history were noncontributory.

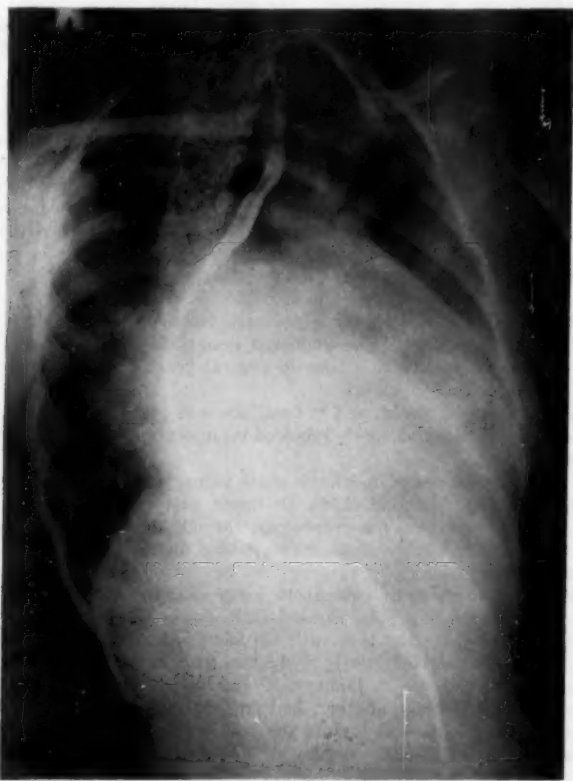


FIG. 3. Case 2. Right oblique view shows marked displacement of the esophagus posteriorly and to the right by the greatly enlarged left auricle.

Physical examination at that time showed a thin woman in acute respiratory distress. Her skin was slightly cyanotic. There was no venous distention. Her entire chest heaved with each heart beat, and the right upper chest expanded with each ventricular systole. Respirations were rapid but the lungs were clear. The apex impulse was visible over a large area at the left anterior axillary line in the sixth and seventh interspaces. The heart was greatly enlarged to percussion in a globular fashion to both the left and the right. There was an apical diastolic thrill.

The heart was absolutely irregular, with a ventricular rate of 90 per minute. The heart sounds were loud, with P_2 louder than A_2 . A rough Grade III apical diastolic murmur was present. A systolic Grade III musical murmur with no radiation, loudest at the apex and in the left fourth interspace, was heard. At the aortic and pulmonic areas it was blowing and of Grade II intensity. The blood pressure was 110/80 mm. of Hg. The abdomen showed no abnormalities, and the liver and spleen were not palpable.

Laboratory examinations showed a red blood cell count of 4,710,000 per cubic millimeter, with 14 gm. of hemoglobin. The white blood cell count was 10,800 per cubic millimeter, with 71 per cent polymorphonuclears, 27 per cent lymphocytes and 2 per cent monocytes. The sedimentation rate was normal, and serologic tests for syphilis were negative. The electrocardiogram was abnormal in that it showed auricular fibrillation, right axis deviation, ventricular strain and digitalis effect.

A diagnosis was made of rheumatic heart disease with auricular fibrillation, mitral stenosis, mitral insufficiency, and questionable pulmonic insufficiency and chronic congestive heart failure. Subsequent radiographic and fluoroscopic examination of the chest showed extreme enlargement of the cardiac shadow, which occupied three fourths of the widest diameter of the thoracic cage. The barium-filled esophagus was displaced far to the right of the midline and posteriorly by giant enlargement of the left auricle. All the other chambers were enlarged to a considerably lesser extent. The lung fields were remarkably clear (figures 2 and 3).

She was placed on an acid ash, low salt diet, and given periodic injections of a mercurial diuretic and small doses of phenobarbital. After a brief period off digitalis she was redigitalized. She improved remarkably and was even able to do part of her housework for the first time in several years. She was able to lie flat, and had no further suicidal thoughts.

She lived on a nearby desert, and at times she was given salt because of probable low-salt syndrome. She subsequently required no injections of mercurial diuretics for many months.

In mid-1948 she developed indefinite chest pains, which only later were shown to be related to eating. In July, 1949, an upper gastrointestinal x-ray series was reported as normal; however, the esophagus was not then carefully examined. In November, 1950, she had episodes of regurgitating undigested food. It is felt that these symptoms were caused by pressure on her esophagus by the enlarged left auricle. This was confirmed by subsequent x-ray examinations.

Follow-up electrocardiographs showed little change, and in the five years that she has been followed there has been little apparent increase in her heart size.

Case 3. A white married female of 40 was first seen by one of us (R. C. P.) because of increasing dyspnea in January, 1947. Her development had been normal, with no history of cyanosis. She had had frequent tonsillitis until a tonsillectomy was done at the age of six. As a child she had had frequent spontaneous epistaxis. She had scarlet fever at the age of six. A diagnosis of rheumatic fever was made at the age of 15, with no subsequent history of recurrent activity. For many years she was a professional dancer, and was asymptomatic until the age of 32, at which time she became excessively tired and short of breath. She was subsequently placed on digitalis, which she continued to take almost continuously until her death. Although she had dyspnea on exertion, orthopnea, and episodes of coughing with rare, mild hemoptysis, she was able to perform her duties as a housewife. She did quite well for seven years, until January, 1947, when her dyspnea and orthopnea became progressively worse. She developed abdominal swelling, edema of the hands and feet and scant urination.

Upon examination she did not appear acutely ill despite her complaints. Neck vein distention was evident and respirations were increased.

Examination of the lungs revealed no unusual signs. She showed a heaving pulsation of her entire chest. A systolic expansion of the right anterior chest was visible. The area of cardiac dullness was greatly enlarged, extending to the left anterior axillary line and to the right midclavicular line. There was a diastolic apical thrill. The rhythm was absolutely irregular, with a ventricular rate of 104. The heart sounds were loud, with P_2 accentuated. A Grade IV rough diastolic murmur was heard over the entire anterior chest, loudest at the apex. A blowing Grade III systolic murmur was also audible over the entire precordium, and was also loudest at the apex. The blood pressure was 140/110 mm. of Hg. Auricular fibrillation was evident. There was no ascites. The liver was tender and enlarged to the level of the umbilicus, but was not pulsatile. There was no cyanosis or peripheral edema.

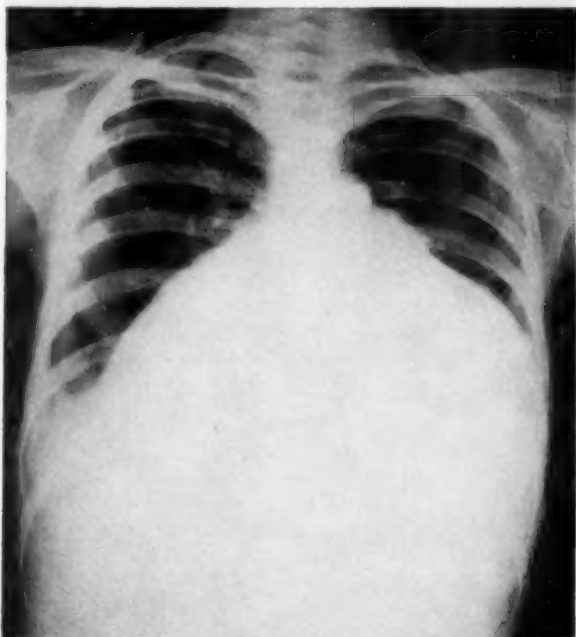


FIG. 4. Case 3. Greatly enlarged and globular shaped cardiac shadow due to combined right and left auricular enlargement.

Laboratory examinations showed a red blood cell count of 4.6 million and 14 gm. of hemoglobin. The white blood cell count was 5,500, with 62 per cent polymorphonuclears, 36 per cent lymphocytes and 1 per cent eosinophils. The urine was alkaline, with a specific gravity of 1.017. No sugar, albumin or abnormal sediment was present. The electrocardiogram showed auricular fibrillation, with a ventricular rate of 100, right axis deviation and digitalis effect. A chest x-ray showed a greatly enlarged cardiac shadow with a globular shape (figures 3 and 4).

A diagnosis was made of chronic rheumatic heart disease with auricular fibrillation, mitral stenosis and insufficiency, possible tricuspid insufficiency, and congestive failure.

The patient was put on an acid ash, low salt diet, maintained on digitalis, and given ammonium chloride with periodic injections of mercurial diuretics. Her symptoms improved markedly on this treatment, although she had virtually no cardiac reserve. A month later she began having frequent back pain just medial to the right scapula. This was very troublesome and was not explained until its relationship with swallowing became evident a year later. In January, 1948, a barium swallow showed compression and posterior displacement of the esophagus in the right oblique

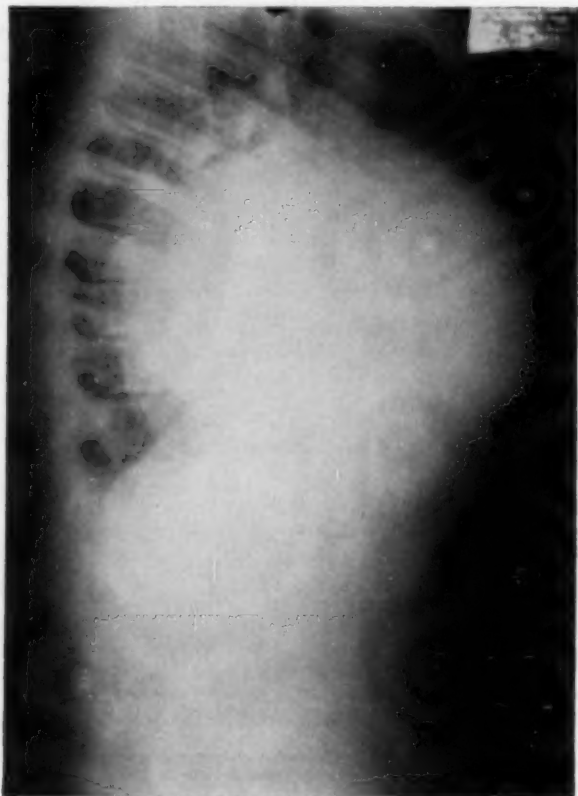


FIG. 5. Case 3. Lateral view shows the marked enlargement of the cardiac shadow both anteriorly and posteriorly.

view and deviation to the right on the posterior-anterior view. The flow of barium was retarded as it passed posterior to a tremendously enlarged left auricle. It was further noted that as the barium passed this area the patient experienced pain in her back.

Subsequently her condition deteriorated slowly. She was almost completely bedridden and required repeated hospitalizations. She had repeated upper respiratory infections, occasional digitalis intoxication and one episode of probable low-salt syn-

drome. She also had dysuria, urinary frequency, backache and fever on at least two occasions. Urinalyses revealed pyuria with a urine culture revealing a streptomycin-sensitive, gram-negative bacillus. Treatment with this drug resulted in apparent cure at that time.

Her condition through 1949 remained much the same and she required several more periods in the hospital. In August, 1950, a chest x-ray showed further enlargement of the heart. In October, 1950, she was involved in an automobile accident and suffered a severe head injury with a basal skull fracture, subarachnoid hemorrhage and intracerebral hemorrhage. Despite being unconscious for a week she survived, but was left with a left third nerve paralysis and with marked personality and memory changes. She became exceedingly difficult to manage because of confusion. During



FIG. 6. Case 3. Photograph of the heart. Note the massive dilatation of both auricles. Hypertrophied left ventricle opened.

the ensuing year she gradually went further downward and developed anasarca and wasting.

In January, 1952, she was transferred to the San Bernardino County Hospital, where she remained until her death nine months later. Physical examination, repeat chest x-rays and electrocardiograms showed no essential change. Laboratory examinations during this time showed negative serologic test for syphilis, normal non-protein nitrogen, mild albuminuria, serum albumin of 4.5 gm. and serum globulin of 3.0 gm. On one occasion she developed a thrombophlebitis which was successfully treated with anticoagulants. Several thoracic and abdominal paracenteses were productive of transudative fluid. Because of the increasing cardiac enlargement it

was felt by some observers that a possible pericardial effusion was present. Pericardial taps attempted on three occasions resulted only in pure blood. In September, 1952, her dyspnea, anasarca and confusion increased and she died.

Autopsy Findings: The body was that of a 46 year old white female in a good state of nutrition. There was a marked pitting edema of both lower extremities and of the lower half of the abdomen and lumbar region. The external genitalia were markedly edematous, as were both hands.

Abdominal Cavity: The abdominal cavity was filled with a light yellow clear fluid, approximately 2,000 c.c. The lower edge of the liver extended 10.5 cm. below the xiphoid process and 7 cm. below the right costal margin. The pericardial sac



FIG. 7. Case 3. Photograph illustrates the marked deformity and stenosis of the mitral valve. The dilated left auricle is apparent.

was markedly dilated, occupying most of the thorax. It extended from the right anterior axillary line to the left posterior axillary line. The enlarged pericardial sac with its contents produced a moderate compression atelectasis of the lungs, particularly of the left upper lobe.

The pericardial sac was free and contained about 50 c.c. of clear fluid.

Heart: The heart weighed 524 gm. The epicardium was smooth and glistening. Most of the enlargement of the heart appeared to be due to the dilated auricles (figure 6). The right auricle measured 31 cm. in circumference and 16 cm. in vertical diameter. The left auricle was slightly larger, measuring 34 cm. in circumference and 15 cm. in vertical diameter. The wall of the left ventricle measured 14 mm. in thickness, and the wall of the right ventricle measured 2 mm. The wall of the left

auricle measured 10 mm. in thickness, and the wall of the right auricle measured 10 mm. in thickness; the inner lining was everywhere smooth. In the appendage of the right auricle an adherent thrombus was present. The mitral valve showed a marked fibroplastic deformity; the chordae tendineae were markedly shortened and thickened, and the valve had the typical appearance of a "fish-mouth" stenosis (figure 7). The free margins of the valve were rigid and calcified, and the ostium was markedly stenosed, barely admitting the tip of the small finger. The tricuspid valve measured 35 mm. in circumference and showed a slight thickening of its free margins, and admitted two fingers. The aortic valve measured 60 mm. in circumference, and the pulmonic valve measured 65 mm. in circumference.

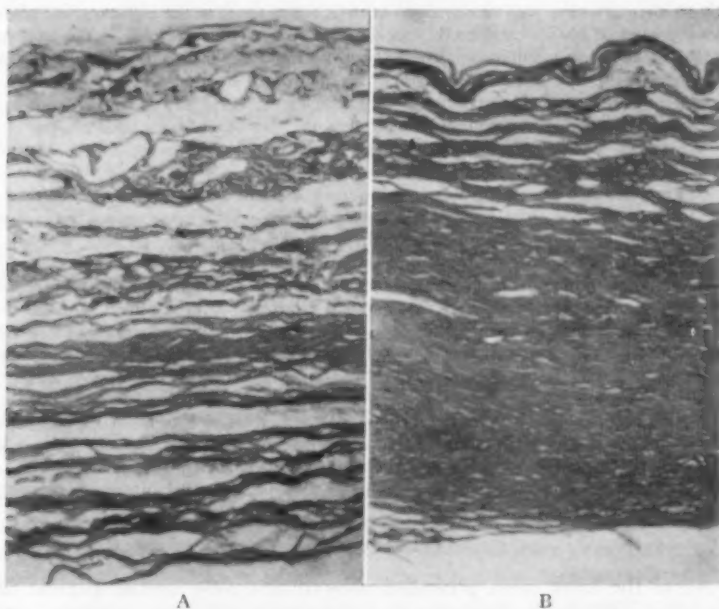


FIG. 8. Photomicrographs of the wall of the right auricle (A) and left auricle (B) (same magnification $\times 240$). The thickness of the walls is similar, while the fibrosis in the left auricle is more condensed. The right shows much edema and fibrosis.

Liver: The liver weighed 1,260 gm. The surface appeared finely nodular and the capsule was thickened. On sectioning, the surface was a reddish brown with distinct markings.

Stomach: The mucosa was somewhat atrophic and the blood vessels appeared prominent.

Spleen: The spleen weighed 700 gm. There was a single healed infarct present, and the sectioned surface appeared deeply hyperemic.

Right Kidney: The right kidney weighed 75 gm.; it was small; the capsule stripped with difficulty, leaving a granular and scarred surface.

Left Kidney: The left kidney weighed 240 gm.; the capsule stripped with moderate difficulty, leaving a granular surface in which there were several scarred, de-

pressed areas. On sectioning, the cortex averaged 6 mm.; there was no dilatation of the pelvis or calices.

Urinary Bladder: The bladder was slightly dilated and contained clear urine.

Intestinal Tract: There was some edema of the small bowel; the large bowel showed no changes.

Brain: The brain weighed 1,360 gm. In the region of the right temporal lobe there was a large area of softening measuring 3 cm. in diameter, and in the region of the right frontal lobe there was a depressed area of softening measuring 4 cm. These areas were discolored light yellowish brown and were not of recent origin.

Microscopic Findings: Section from the left auricle showed marked fibrosis of the wall, with almost complete replacement of muscle fibers; the wall was insignificantly thicker than the wall of the right auricle. The wall of the right auricle showed a lesser degree of fibrosis and there was some edema. The arterioles in the wall were slightly thickened but patent (figure 8). A section taken through the mitral valve showed extensive hyalinization and some calcification. Sections from the wall of the left ventricle revealed hypertrophy of the muscle fibers. There were focal areas of fibrosis, particularly surrounding blood vessels. No Aschoff's nodules were noted. The arterioles were moderately thickened but their lumens were free. No acute inflammatory changes were noted.

Section through the tricuspid valve showed increased fibrosis.

Section from the liver revealed a marked periportal fibrosis, often interrupting the lobules of cells. The sinuses were dilated and hyperemic. There was an insignificant bile duct proliferation. The changes indicated cardiac cirrhosis.

Sections of the brain in the region of softening showed spicules of atrophic bone.

Anatomic Diagnosis: Massive symmetrical dilatation of both auricles of the heart. Moderate hypertrophy of both ventricles. Severe fibrocalcific deformity of the mitral valve, with marked stenosis and insufficiency. Moderate fibroplastic thickening of the tricuspid valve, with slight stenosis and insufficiency. Compression atelectasis of both lower pulmonary lobes, and emphysema of the remaining lobes. Post-traumatic encephalomalacia in the right temporal and frontal lobes. Atrophic cardiac cirrhosis of the liver. Thrombus in the appendage of the right auricle. Hypoplasia and severe nephrosclerosis of the right kidney. Hyperplasia and sclerosis of the left kidney. Pulmonary infarction in the right lower lobe. Healed infarct in the spleen.

DISCUSSION

All of the three cases presented showed relatively similar clinical characteristics. While the diagnosis was suspected in all of the instances, operation in one case and autopsy in another confirmed the clinical impression. The following resumé of the outstanding characteristics of this condition, taken from these cases and others previously reported, will help clarify some of the salient features of the anatomic and pathologic findings, the common symptoms and signs, the usual radiologic appearance and the disturbances in physiology involved.

Anatomy: The left auricle can attain greater dilatation than any other heart chamber due to its thin walls, its anatomic position, the lack of safety valves into the great veins such as occur on the right, and the fact that both ventricles may pump blood into the chamber in mitral insufficiency. The left auricle is the most superior chamber of the heart and lies posteriorly. The esophagus lies directly behind the auricle and is in contact with the peri-

cardium for several inches. The trachea bifurcates above the auricle and the left bronchus may rest on it for a short distance. In marked dilatation the auricle fills the space beneath the arch of the aorta, which passes over, then down, behind, and to its left.

There may be clockwise rotation of the heart due to both the left auricular enlargement and the right ventricular hypertrophy which is commonly associated. This causes the left ventricle to lie more posteriorly and to the left. Thus, because of the aortic arch and left ventricle on its anterior and left posterolateral aspects, and the spine behind, the auricle can only enlarge to the right in an upward and forward direction. The right auricle subsequently lies slightly below and anterior to the left auricle. The right lung can thus be easily compressed towards the right axilla by the expanding auricle.

Clinical Characteristics: Although the ultimate diagnosis of a massive left auricle is to a great extent dependent on the roentgenologic findings, there are sufficient common clinical features which should suggest the diagnosis.

A. History: The majority of cases have a good history of previous rheumatic fever and present the usual findings characteristic of chronic rheumatic carditis and mitral valvulitis. Massive dilatation of the left auricle is more common in female than in male patients, in a ratio of more than two to one, a distribution conforming to that of mitral valvular disease. Our three cases were all females in the third and fourth decades. There is a frequent complaint of pain or difficulty in swallowing. A number of cases with dysphagia as a prominent symptom have been reported.^{13, 16, 3, 17, 18} This is undoubtedly caused by the compression and angulation of the esophagus by the enlarged auricle. Chest pain is quite common and shows a great variety of types. Usually there is pain in the right side of the chest, with radiation to the right scapula or shoulder. Rarely, the pain may be present in the left chest. It is usually described as an aching or stabbing type of pain. In one case the pain was determined to be due to spinal erosion, a rare occurrence.⁵ In general the cause of the pain is obscure, although it has been postulated that it may be due to a disproportion between the available blood supply and the metabolic demands of the expanded auricular wall, since the pain frequently occurs with exercise.⁸ Episodes of syncope have been reported. Partial vocal cord paralysis, due to involvement of the left recurrent laryngeal nerve, and hoarseness have also occurred. A dry, nonproductive cough is frequently found and is apparently due to pressure upon the left bronchus or tracheal bifurcation, or to compression of the right lower lung by the enlarged auricle. A remarkable feature, repeatedly noted, is the relatively great amount of exercise tolerance the majority of these patients possess, a fact probably due to the infrequent occurrence of pulmonary hypertension. This was seen in the first case, where cardiac catheterization revealed little pulmonary hypertension. Parkinson⁴ stated that "massive left auricular enlargement possessed clinical features of great interest, such as the moderate

symptoms which may accompany a heart so hugely dilated, a clinical contrast with the patient so ill with a comparable ventricular enlargement, as from hypertension." Why little or no pulmonary hypertension exists in the face of a tremendous left auricle still remains obscure. Perhaps the hugely dilated chamber, which may contain up to 1.5 L. of blood, is able to "absorb" that amount of blood which would be borne by the pulmonary vessels, as occurs in the usual case of mitral stenosis with only mild or moderate auricular enlargement. Nichols and Ostrum¹⁸ suggest that even with narrowed mitral orifices the resultant high intra-auricular tension will enable the ventricles to become adequately filled during diastole, and thus the heart can maintain an efficient output as long as the ventricular myocardium remains efficient. All of our patients were capable of greater activity than one sees in the usual advanced case of rheumatic valvulitis.

When the left auricle has dilated to the right, dullness may be percussed at varying intervals to the right of the sternum as far as the axillary line. Dullness at the right posterior lung base is commonly present. It is these factors which have led to the erroneous diagnosis of right pleural effusion in some cases. Mitral valve insufficiency is present in the majority of cases, with or without stenosis. A prominent diagnostic sign is the appearance, over the area of right anterior chest dullness, of a palpable and visible systolic pulsation due to the force of ventricular regurgitation through the open mitral valve. A systolic murmur may also occasionally be heard here. The majority of patients have both apical systolic and diastolic murmurs, which are harsh and loud, and an apical diastolic thrill. Auricular fibrillation is a universal finding. The frequency of auricular fibrillation is easily understandable in the light of the marked fibrosis and thinning of the auricular chamber wall, leaving little or no auricular muscle tissue. Only two reported cases showed reversion to a normal rhythm for short periods.

As a rule, evidence of right sided failure is lacking. Hydrothorax, elevated venous pressure, ascites, hepatic engorgement and dependent edema are late in appearance.

Radiologic Appearance: The left auricle may appear as part of the upper and right border of the heart by careful x-ray examination long before signs of unusual enlargement are evident on physical examination.^{24, 14, 15, 19} Bordet¹⁵ found extension of the left auricle to the right in 5 per cent of 200 cases of mitral stenosis. The auricle is sometimes seen as a dense shadow within the cardiac silhouette in a posteroanterior view. Early, a "double-contour" may be present, with superimposition of the left and right auricular shadows. Although it was first described by Gabert in 1924,²⁰ Steele and Patterson in 1928¹⁹ emphasized the distortion of the left bronchus as an index of left auricular enlargement. Elevation of the left main bronchus is always found, sometimes with accompanying compression. Distortion of the normal esophageal course is well known in auricular enlargement.^{12, 13} In the right oblique positions the enlarged left auricle shows gradual en-

croachment upon the midportion of the retrocardiac space. In massive enlargement there is usually total obliteration of this space. One sees the barium-filled esophagus displaced posteriorly, with occasional delay in the passage of the barium. An exaggeration of the normal right deviation of the esophagus is seen in the greatest majority of cases. In the first case described here, and in two other reports, deviation to the left has been found.^{12, 14} Schwedel¹⁴ states that this may be due to (1) a normal eccentric position of the esophagus; (2) concurrent right auricular and ventricular enlargement, or (3) esophageal adhesions as might occur in an associated mediastinitis, or adhesions due to an enlarged horizontal portion of the aortic arch. The left ventricle in most of the reported cases is greatly hypertrophied, and in our three cases was quite large.

Fluoroscopically, the right side of the heart shows diminished pulsation compared to the left. Also, fluoroscopy verifies that the upper curve on the right is identical with the posterior superior curve of the heart. Differential diagnosis would include mediastinal tumor, aortic aneurysm, pericardial cyst, primary tumor of the heart or lungs, and pleural and pericardial effusion.

Angiocardiographic methods and cardiac catheterizations in selected cases may be necessary for differentiation.

The electrocardiogram shows no characteristic pattern except auricular fibrillation, right axis deviation and marked clockwise rotation. Precordial leads over the right chest show little electrical activity. Obviously considerable variation will be present because of the nature and degree of anatomic variability.

The etiology of massive left auricular enlargement has been a subject of considerable discussion. As found in our autopsied case and in many others, several factors seem contributory to the production of such unusual findings.^{5, 17, 18, 27, 30} Although the mechanical factor of mitral stenosis was originally thought to be the main feature, this has been discarded. Considering how commonly mitral insufficiency and stenosis exist, massive dilatation of the left auricle is rarely seen. Bramwell and Duguid,¹¹ Nichols and Ostrum¹⁶ and Parsonnet¹⁷ emphasize that an auriculitis of rheumatic origin, with resultant fibrosis of the auricular wall, is one of the most important factors in the production of a massive left auricle. The adjacent pericarditis frequently found gives further evidence of severe localized rheumatic involvement. In our autopsied case and in others reported, fibrous replacement of the auricular muscle has been almost complete. Destruction of the normal tissue results in loss of elasticity, with thinning and weakness of the wall. The existence of mitral insufficiency either with or without stenosis allows a great burden to be thrown on the left auricular wall. This marked increase in auricular pressure with each ventricular systole in the face of mitral valvulitis and a fibrosed auricular wall probably are the major combined factors in producing massive left auricular enlargement. In our

case with the huge bilateral auricular enlargement, similar pathologic changes in the right auricular wall along with a tricuspid insufficiency and hypertrophied right ventricle would lend further credence to the correctness of the proposed etiology. As far as treatment is concerned, it is no different from that of any other case of rheumatic valvular disease. Digitalis and symptomatic care are usually required. The use of quinidine for conversion of the auricular fibrillation will probably be of no avail.

SUMMARY

Two cases of unusual massive dilatation of the left auricle and one case of huge combined left and right auricular enlargement are presented. In all cases, chronic rheumatic heart disease was present along with mitral insufficiency and stenosis and auricular fibrillation. The diagnosis of massive left auricular enlargement should be suspected if in the usual case of chronic rheumatic heart disease one finds dysphagia, cough, chest pain, persistent auricular fibrillation, good exercise tolerance relative to the greatly enlarged heart, visible and palpable systolic pulsation of the right chest wall, and the typical x-ray findings. It is proposed that this condition is probably more common than reports would indicate. The importance of correct diagnosis is stressed. A discussion of the anatomy, physical signs, symptoms, radiologic picture, pathology and probable pathogenesis is presented.

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SCLERODERMA: RELATION OF PULMONARY CHANGES TO ESOPHAGEAL DISEASE*

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SCLERODERMA is a systemic disease involving the collagenous tissues. The skin, gastrointestinal tract, and the cardiovascular, musculoskeletal, genitourinary and pulmonary systems may be involved. Dysphagia is a common complaint with esophageal involvement. The purpose of this report is to evaluate the lung changes in the cases reported in the literature, to add our own experience in 16 patients and to examine the relationship of the pulmonary changes and dysphagia.

REVIEW OF LITERATURE

The first authenticated cases of pulmonary lesions with generalized scleroderma were described by Matsui¹ in 1924. He reported six post-mortem cases, two of which had fibrosis of the lungs. In 1941 Murphy, Krainin and Gerson² described a patient whose pulmonary manifestations constituted the dominant aspects of the disease. The following year the classic paper by Klemperer, Pollack and Baehr³ established scleroderma as a collagen disease involving many organs. In 1943 Weiss, Stead, Warren and Bailey,⁴ discussing scleroderma heart disease, mentioned pulmonary changes as an incidental finding. Getzowa⁵ in 1945 published the pulmonary pathologic changes in great detail. In 1948 Lloyd and Tonkin⁶ reviewed the literature (which then totaled 17 cases with pulmonary changes), and added four more cases. In a recent report Spain and Thomas⁷ evaluated pulmonary function in patients with scleroderma. Since that time many isolated reports have appeared.⁸⁻²² In 1952 Hayman and Hurt²³ reported pulmonary fibrosis associated with scleroderma in a coal miner, and reviewed 27 cases reported in the English literature.

MATERIAL

Only cases with pulmonary changes were selected for this study. Common among these was scleroderma of the skin. Many of the cases had multiple systems involved, but only the association of esophageal disease was noted specifically. The occurrence of cardiovascular disease secondary to the pulmonary changes (*cor pulmonale*) could not be evaluated effectively because of the failure in most cases to differentiate primary scleroderma of the myocardium.

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A total of 41 cases was collected from the literature (table 1). To this 16 of our own cases were added (table 2). Females predominated—44 (77 per cent) to 13 males (23 per cent). The first symptom in the majority of cases was Raynaud's phenomenon, followed by skin manifestations. The ages at which the pulmonary lesions were first recognized ranged from 17 to 65 years, the majority being in their fourth and fifth decades. Pulmonary disease was the first manifestation of scleroderma in several cases, while in others it did not occur for many years. There was no relationship between the degree of the pulmonary disease and the duration of scleroderma.

PULMONARY DISEASE

The severity of the pulmonary disease varied from no symptoms to severe dyspnea and cyanosis. The majority had exertional dyspnea. Cough was present in some, but as a rule was not very common. Recurrent attacks of "pneumonitis," "pleurisy" or pneumonia occurred in several patients. The most common physical finding was râles at the bases. Cyanosis of the nail-beds was frequent, but this was probably due to the local anoxia of Raynaud's phenomenon rather than to pulmonary disease.

FUNCTIONAL ASPECTS

Pulmonary function studies have been meagre except for vital capacity measurements. Spain and Thomas⁷ studied one patient completely (case 34) and found that, while the vital capacity, residual air and lung volume were decreased, the maximal breathing capacity was within normal limits. The O₂ saturation of arterial blood was markedly decreased during exercise. Baldwin, Cournand and Richards²⁴ reported the same patient in addition to three other patients with scleroderma and noted the same pulmonary function findings. They concluded that the respiratory disease was due to alveolar respiratory insufficiency with only minimal ventilatory impairment. Lukas²⁵ also found, in two patients, that pulmonary insufficiency was due to alveolar respiratory impairment and not to decreased ventilatory function.

Decompensated cor pulmonale was the cause of death in two patients (cases 34 and 47). Extensive pulmonary fibrosis with pulmonary hypertension and right heart failure were the predominant clinical features, and at post mortem an enlarged right ventricle without myocardial lesions due to scleroderma was present. Another patient (case 45) studied by Lukas²⁵ had pulmonary hypertension, right axis deviation of the electrocardiogram and an enlarged pulmonary artery on angiocardiography (figure 3B).

ROENTGEN ASPECTS

The roentgen changes in scleroderma consist of mottling of the lung parenchyma indistinguishable from pulmonary fibrosis (figures 1 to 4) and usually occurring at the bases. In four patients (cases 29, 30, 31 and 41)

TABLE I
Pulmonary and Esophageal Findings in Scleroderma

Case No.	Author	Age and Sex	Type and Time of Onset	Signs and Symptoms	Chest X-ray	Esophageal Findings	Autopsy Findings	Remarks
1	Matsui ¹ 1924	17 F	Not reported	Skin changes, dyspnea	Not reported	Not reported	<i>Lungs:</i> Vascular changes, fibrosis of alv. septa. <i>Esophagus:</i> Atrophy, fibrosis of muscularis	
2	Ibid.	48 F	Raynaud's 5 yrs.	Raynaud's phenomenon, skin changes	Not reported	Not reported	<i>Lungs:</i> Pulm. artery dilat., arterioles thickened, fibrosed except for apices. <i>Esophagus:</i> Atrophy and fibrosis of muscularis	
3	Ibid.	19 F	Raynaud's phenomenon	Skin changes, Raynaud's phenomenon, tbc.	Not reported	Not reported	<i>Lungs:</i> Massive tbc. Fibrosis of muscularis of esophagus	
4	Lilienthal ² 1941	45 F	Raynaud's phenomenon 12 yrs.	Skin changes, progressive dyspnea, pneumonia. No G.I. history given	Diffuse mottling in lower half of both lung fields	No exam.	No autopsy	
5	Ibid.	39 F	Raynaud's 13 yrs.	Skin changes, Raynaud's, dyspnea. No G.I. history given	Exaggerated markings at both lower lung fields	None	Death due to resp. failure. No autopsy	
6	Ibid.	30 F	Raynaud's 3 yrs.	Skin changes, No G.I. history given	Mottling at both bases	None	Death due to pneumonia. No autopsy	
7	Murphy ³ 1941	30 F	Not reported	Skin changes, dyspnea, cough	Bilat. pulm. strandlike infiltration, mostly at bases	Not reported	No autopsy	

TABLE 1—Continued

Case No.	Author	Age and Sex	Type and Time of Onset	Signs and Symptoms	Chest X-ray	Esophageal Findings	Autopsy Findings	Remarks
8	Weiss ⁴ 1943	24 F	Raynaud's 2 yrs.	Skin changes, cardiac failure, cough, occasional vomiting	Congestion of lungs	No exam.	Areas of pulm. fibrosis. No G.I. changes	
9	Ibid.	55 F	Raynaud's 1 yr.	Skin changes, orthopnea, occa- sional vomiting	Congestion, fibrosis	No exam.	Bronchopneumonia, fibrosis; no G.I. changes	
10	Ibid.	54 F	Raynaud's 25 yrs.	Skin changes, dyspnea, <i>dysphagia</i>	Mottling at both bases	Constriction of esophagus above diaphragm	No autopsy	
11	Ibid.	56 M	Joint pain 2 yrs.	Skin changes, cough	Diffuse mottling at both bases	No changes	No autopsy	
12	Ibid.	35 F	Raynaud's 16 yrs.	Skin changes, <i>dysphagia</i>	Increased pulm. markings	Narrow con- striction of lower 1/4 of esophagus	No autopsy	
13	Jackman ⁹ 1943	55 F	Skin changes 13 yrs.	Raynaud's, "heaviness" in chest, hypertension	Coarse fibrosis of left upper and rt. lower lobes	8 hr. barium retention in esophagus	No autopsy	
14	Ibid.	46 F	Raynaud's 6 mos.	Skin change, wt. loss	Pulm. fibrosis, both lower lobes	None	Lungs: Interstitial and periva- cular fibrosis; mucosal and submucosal fibrosis of stomach and colon	
15	Pugh ¹⁰ 1945	40 M	Raynaud's 2 yrs.	Skin changes, dyspnea, <i>dysphagia</i>	Marked fibrosis of both lower lung fields	Esophagus rigid, dilated without peristalsis	No autopsy	

TABLE I—Continued

Case No.	Author	Age and Sex	Type and Time of Onset	Signs and Symptoms	Chest X-ray	Esophageal Findings	Autopsy Findings	Remarks
16	Dostrowski ¹¹ 1947 Getzowa ⁸ 1945	21 M	Skin changes 7 yrs.	Weakness, cough, skin changes	Scattered opacities	No exam.	Lysis and sclerosis of alveolar walls, cystic bronchiolar hyperplasia replacing the alveolar parenchyma	
17	Ibid.	34 F	Skin changes 1 yr.	Jt. pain, skin changes	Inc. pulm. markings	No exam.	Lysis and sclerosis of alveolar walls, cystic bronchiolar hyperplasia replacing the alveolar parenchyma	
18	Ibid.	21 F	Skin changes 7 yrs.	Respiratory difficulty, cough, skin changes	Inc. markings, scattered opacit. prob. tbc.	No exam.	No autopsy	
19	Rebans ¹⁰ 1945	36 F	Skin changes 15 mos.	Anorexia nervosa and vomiting, abdominal cramps, edema, intestinal obstruction	No abnormality	No exam.	Congestion at bases, fibrosis and vascularity of both lower lobes, many alveoli lined with bronchiolar epithelium. <i>Esophagus:</i> Many layers replaced by fibrinoid	
20	Ibid.	56 M	Raynaud's 1 yr.	Dyspnea, cough, <i>dysphagia</i>	Bilat. root branch thickening towards bases. Slight pleural thickening	No abnormality	Vascular fibrosis in both lower lobes, thickening of blood vessels. G.I. tract extensive changes in muscle layers	
21	Goetz ¹¹ 1945	42 F	Raynaud's 20 yrs.	<i>Dysphagia</i> , skin changes, dyspnea, cyanosis	Abnormal streaks and densities rt. lower zone	Tubular distal contraction with proximal dilat. of esophagus	Pneumonia, fibrous strands. G.I. confirms x-ray finding	Author has 13 cases; reports only this one

TABLE I—Continued

Case No.	Author	Age and Sex	Type and Time of Onset	Signs and Symptoms	Chest X-ray	Esophageal Findings	Autopsy Findings	Remarks
22	Bourne ¹² 1947	56 F	Raynaud's 22 yrs.	<i>Dysphagia</i> , skin changes	Bilateral basal fibrosis	Dilated esophagus, hiatus hernia	No autopsy	
23	Ibid.	60 F	Raynaud's 25 yrs.	<i>Dysphagia</i> , skin changes	Fibroid change in rt. apex	No exam.	No autopsy	
24	Lloyd ^a 1948	48 F	Raynaud's 6 yrs.	Skin changes, dyspnea	Severe fibrosis both lower lobes	No exam.	No autopsy	Vital capacity 27%
25	Ibid.	48 F	Raynaud's 20 yrs.	Skin changes, dyspnea, <i>severe dysphagia</i>	General fibrosis predominant at bases	No exam.	No autopsy	
26	Ibid.	55 M	Exertional dyspnea 3 yrs.	Skin changes	Widespread fibrosis predominant at bases	No exam.	No autopsy	
27	Ibid.	48 F	Raynaud's 13 yrs.	Skin changes, dyspnea	Generalized fibrosis, mostly lower bases	No exam.	No autopsy	
28	Wigley ¹³ 1949	56 M	Exertional dyspnea	Skin changes, dyspnea, basal rales. No G.I. history given	Network of dense shadows, more at bases	None	No autopsy	
29	Aronson ¹⁴ 1950	43 F	Raynaud's 18 yrs.	Skin changes, indigestion, <i>dysphagia</i> , exertional dyspnea, melena	Parenchymal opacities, particularly lt. lower lobe, honeycomb pattern	Constriction of distal end with proximal dilatation of esophagus	<i>Lungs:</i> Small cysts with fibrous tissue in both lower lobes	

TABLE 1—Continued

Case No.	Author	Age and Sex	Type and Time of Onset	Signs and Symptoms	Chest X-ray	Esophageal Findings	Autopsy Findings	Remarks
30	Church ¹⁷ 1950	49 F	Raynaud's phenomenon 14 yrs.	Skin changes, <i>dysphagia</i> , pleurisy	Diffuse fibrosis with fine cystic outline, particularly at bases	None	No autopsy	
31	Ibid.	49 F	Raynaud's phenomenon 14 yrs.	Skin changes, <i>dysphagia</i> , cough	Rt. lower lobe and rt. middle lobe consolidation with subsequent cystic changes	Tapering constriction at lower end of esophagus	No autopsy	
32	Kraus ¹⁸ 1950	55 M	Raynaud's 8 yrs.	Pneumonia twice, skin changes, <i>dysphagia</i> , severe	Bilateral fibrosis, mostly basal	Negative G.I. series	No autopsy	
33	Muller ¹⁹ 1950	64 F	Vitiligo, many yrs.	Skin changes, Raynaud's, dyspnea and cough, basal rales	Fine, bilateral linear fibrosis of both lower lobes	No exam.	No autopsy	
34	Spain ⁷ 1950	65 M	Dyspnea, 10 yrs.	Raynaud's phenomenon, skin changes, basal rales	Diffuse reticular shadow at both bases	Not reported	Scleroderma of esophagus, cystic and compact sclerosis of lungs, bronchiectasis	Pulm. function tests: alveolar respiratory impairment
35	Sundin ²⁰ 1950	52 F	Raynaud's phenomenon, skin changes 5 yrs.	Cyanosis, slight dyspnea, <i>dysphagia</i>	Marked basal fibrosis, bilateral	Dilatation of esophagus	No autopsy	

TABLE 1—Continued

Case No.	Author	Age and Sex	Type and Time of Onset	Signs and Symptoms	Chest X-ray	Esophageal Findings	Autopsy Findings	Remarks
36	Dreyer ¹¹ 1951	63 F	Raynaud's phenomenon 25 yrs.	Skin changes, Raynaud's phenomenon 25 yrs.	Bilateral basal and mid lobe fibrosis	Dilatation by x-ray	No autopsy	
37	Gil ¹² 1951	48 F	Raynaud's 5 yrs.	Skin changes, dysphagia, nausea and vomiting	Fibrosis of both lung fields	Proximal dilatation and distal constriction of esophagus and stomach	No autopsy	
38	Ibid.	36 F	Raynaud's phenomenon 6 yrs.	Skin changes, dysphagia, nausea and vomiting	Fibrosis of lungs	Dilatation and stenosis of esophagus and stomach—dilatation of intestine	No autopsy	
39	Ibid.	18 F	Raynaud's 2 yrs.	Skin changes, dysphagia, abdominal pain	Fibrosis of lungs	No exam.	No autopsy	
40	Ibid.	40 M	Raynaud's 14 yrs.	Skin changes, dysphagia	Fibrosis of lungs	Severe dilatation and stenosis of esophagus	No autopsy	
41	Hayman ¹³ 1952	36 M	Raynaud's 8 yrs.	Skin changes, weight loss 40 pounds, anorexia, exertional dyspnea.	Fibrosis more at bases with cysts varying from 1 to 2 cm.	Moderate constriction at lower end with dilatation above.	No autopsy	

TABLE II
The New York Hospital Cases

Case No.	Age and Sex	Type and Time of Onset	Signs and Symptoms	Chest X-ray	G.I. Examination	Autopsy	Remarks
543426 42	60 F	Arthritis 3½ yrs.	Weakness, anemia, skin changes, no dysphagia, severe attacks of pleurisy	Bilateral basilar fibrosis with elevation of rt. diaphragm. <i>Angio</i> : no abnormality	Normal esophagus	Alive	
562091 43	39 F	Raynaud's 8 yrs.	Skin changes, dysphagia, dyspnea	Extensive mottled densities along the vascular markings in both lower lobes	Dilatation with narrowing and tapering at cardia	Alive	
473615 44	36 F	Raynaud's 20 yrs.	Skin changes, dysphagia	Infiltration in lt. lower lobe	Esophagram: Smooth mucosa	Alive	
569329 45	44 F	Raynaud's 10 yrs.	Skin changes, dyspnea, dysphagia, frequent upper respiratory infections	Linear streaky densities, more marked at bases. <i>Angio</i> : Enlargement of pulm. artery, irregularity of peripheral branches	Rigidity with delayed emptying of esophagus	Alive	Mild pulmonary hypertension on cardiac catheterization. Pulmonary insufficiency
574265 46	58 F	Raynaud's 5 yrs.	Skin changes, epigastric pain	Density at lt. costophrenic angle	Dilatation and rigidity of lower ½ of esophagus	Alive	

TABLE II—Continued

Case No.	Age and Sex	Type and Time of Onset	Signs and Symptoms	Chest X ray	G.I. Examination	Autopsy	Remarks
611275 47	63 M	Raynaud's 3 yrs.	Skin changes, <i>dysphagia</i> , no cardio- respiratory symptoms	<i>1st exam.</i> : pulmonary emphysema. <i>1 yr. later</i> : fibrosis of lt. midlung field	Constriction of esophagus	Alive	
331000 48	52 F	Raynaud's 10 mos.	Skin changes	Areas of fibrosis, particularly on rt. Increased markings at bases	No exam.	No autopsy	
472098 49	53 M	Skin changes 1 yr.	Fever, pains, aches, basal râles	Accentuated paren- chymal markings, mostly in rt. lower lung, interstitial fibrosis	G.I. series, esophagram negative	No autopsy	
190136 50	46 F	Raynaud's 2 yrs., vomiting	Skin changes, <i>dysphagia</i>	Increased strandlike areas in both lower lung fields	No exam.	No autopsy	
324258 51	60 F	Raynaud's 1 yr.	Skin changes, epigastric pain, hematemesis, râles at bases	Scoliosis, osteoporosis, bilateral basal fibrosis	Fusiform narrowing of esophagus in mid portion. Distal and irregular narrowing	Alive	
24438 52	60 F	Raynaud's 14 yrs.	Skin changes, indi- gestion, <i>dysphagia</i> , heart failure	Bilateral fibrosis, enlarged heart	Dilatation of esophagus with pointed conical termination at diaphragm		

TABLE II—Continued

Case No.	Age and sex	Type and duration of onset	Signs and Symptoms	Chest X ray	G.I. Examination	Autopsy	Remarks
Bronx Vet's Hospital—Courtesy Dr. Frank Lovelock 53	43 M	Dyspnea 7 yrs.	Skin changes, basal rales, dyspnea. Electrocardiogram showed rt. heart strain pattern	Multiple small nodular fibrosis scattered throughout both lung fields, especially at bases	Dilatation esophagus	Rt. ventricular hypertrophy (cor pulmonale), fibrinous pleura, fibrosis of lungs (diffuse parenchymal), few areas with small cysts and alveolar wall dissolution, intimal proliferation. No lesion in esophagus	Pulmonary function studies, alveolar respiratory insufficiency with reduced lung volume
528866 54	62 F	Raynaud's 25 yrs.	Skin changes, dysphagia	Parenchymal calcified density. No other changes	Slight delay in emptying with dilatation of lower end of esophagus	<i>Esophagus:</i> Thinning with autolysis. <i>Lungs:</i> Increased fibrotic tissue with thickened alveolar walls, areas of proliferation of bronchial epithelium	
7849 55	54 F	Arthritis 5 yrs.	Skin changes, fullness after meals	Fibrosis	No exam.	No autopsy	
576040 56 Courtesy Dr. Raymond Miller	60 F	Skin changes 15 yrs.	Raynaud's syndrome, exertional dyspnea, basal rales, no dysphagia	Fibrosis at both bases, normal angiocardiology	Proximal dilatation with distal narrowing of esophagus	Alive	
576039 57 Courtesy Dr. Raymond Miller	51 F	Dyspnea 6 yrs.	Raynaud's syndrome, skin changes, occasional regurgitation	Fibrosis at both bases, normal angiocardiology	Dilatation with constriction at cardia	Alive	

a "honeycomb appearance" or cysts of various sizes at the bases, is described. Bilateral involvement predominates; in unilateral disease the right side is more often involved. Pugh³³ believes that the pulmonary lesions of scleroderma have a distinctive roentgenographic appearance, and that in many cases the diagnosis can be made without knowledge of clinical data. He concedes, however, that these distinctive features defy adequate description. We were unable in our own cases to recognize any distinctive pattern that

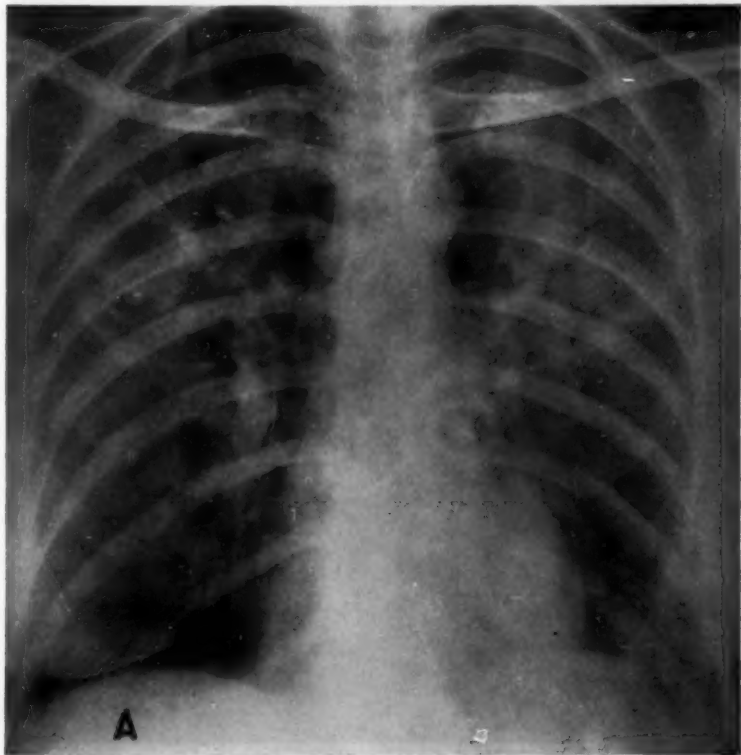


FIG. 1A. Case 44. Reticulonodular densities, especially prominent at bases.

would differentiate the pulmonary fibrosis of scleroderma from that occurring in other diseases. In cases suspected of being complicated by pulmonary hypertension or cor pulmonale, angiocardigraphy is useful to demonstrate enlargement of the pulmonary artery or right ventricle.²⁸

PATHOLOGICAL ASPECTS

Fifteen of the 57 cases were studied at post mortem. In one (case 3) the pulmonary findings consisted of massive fibrocaseous tuberculosis. In

the others the changes were related to scleroderma, and may be divided into two groups. In the first group, comprising half the number, interstitial fibrosis was prominent, the alveolar walls being thickened and sclerosed. Arteriolar thickening with fibrosis was prominent. Intimal proliferation was also a conspicuous feature. The remaining seven cases had, in addition, the lesions first described by Getzowa,⁵ namely, gross and microscopic cystic

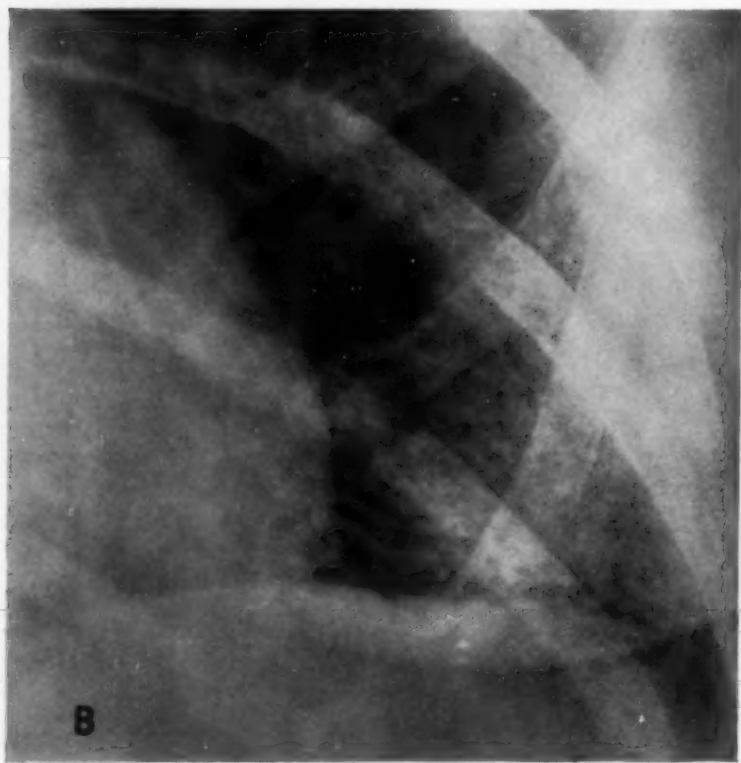


FIG. 1B. Case 44. Enlargement showing changes at left base.

structures. Some of the cysts were formed by the dissolution of alveolar walls and were devoid of epithelium. Most of the cysts, however, were lined by bronchiolar-like epithelium. These cystic structures completely replaced the lung parenchyma in areas. In Getzowa's⁵ cases the cystic changes were very extensive, involving the greater portion of the entire lung. Cases 53 and 54, on the other hand, had predominantly fibrous changes, with only scattered patchy areas of the bronchiolar hyperplasia.

In summary, the predominant lung lesion in scleroderma is fibrosis. The bronchiolar-like cysts are another aspect of this disease which have not been recognized in all cases, possibly because they may be a relatively late change.

ESOPHAGEAL LESIONS

Incidence with Pulmonary Lesions: Esophageal lesions on x-ray or at autopsy and severe dysphagia occurred in 23 (56 per cent) of the cases with pulmonary lesions described in the literature (table 1); in our series, 11

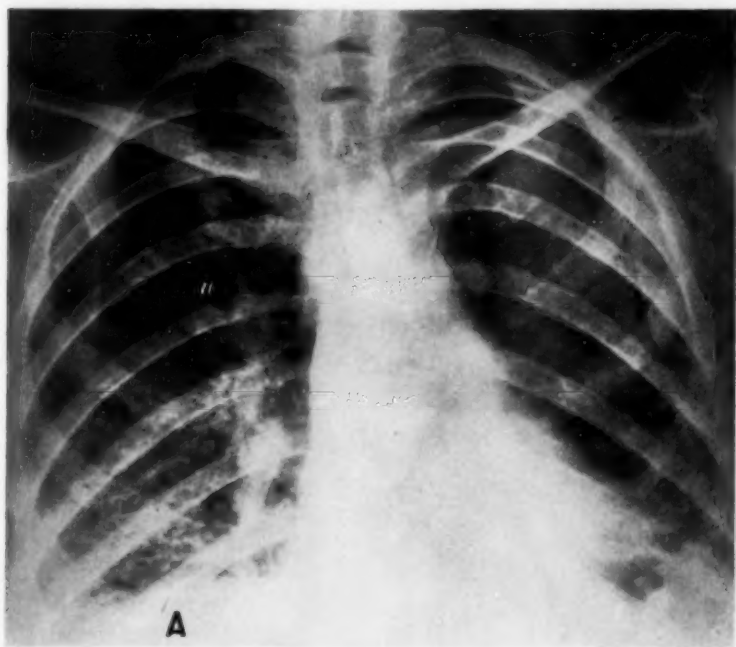


FIG. 24. Case 43. Mottled densities are more pronounced at bases.

(69 per cent) had similar esophageal involvement (table 2). In the literature, however, not all the authors were concerned with dysphagia or esophageal disease.

Incidence with Scleroderma: Recently, Evans²⁷ reported 38 cases of scleroderma. The esophagus was involved in 45 per cent. Hale and Schatzki²⁸ have given an excellent description of the roentgen manifestations of the gastrointestinal tract in 22 patients with scleroderma. They found changes in the esophagus in 13 (59 per cent) of their cases, and emphasized

the fact that some of their patients had minimal or no symptoms referable to the esophagus.

Clinical Aspects: Dysphagia is the most common symptom in esophageal involvement, but indigestion, nausea and vomiting have also been described.^{28, 29}

Roentgen Aspects: The roentgen changes are not constant but follow a recognizable pattern. The transit of barium through the esophagus is delayed. Peristalsis is decreased and may be absent. The proximal two-thirds of the esophagus are often dilated, with the cardiac end frequently

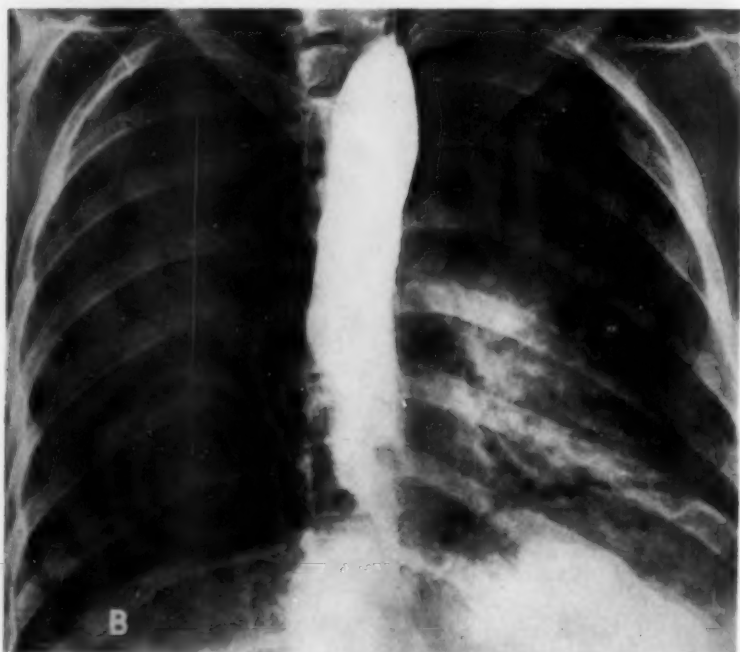


FIG. 2B. Case 43. Esophagram shows a dilated atonic esophagus, with narrowing at cardiac end.

narrowed and rigid. The normal mucosal pattern is lost. The barium may adhere unevenly to the walls of the dilated esophagus. Dilatation is less marked than in cardiospasm. The cardiac end of the esophagus, though narrowed, is patulous and, unlike cardiospasm, allows barium to pass into the stomach (figure 2B).

Pathologic Aspects: Muscle atrophy and replacement by fibrous tissue or fibrinoid sclerosis of the submucosa with occasional loss of the mucosa are the lesions due to scleroderma of the esophagus.¹⁰

DISCUSSION

Dysphagia is common in scleroderma. Because of the association of aspiration pneumonitis and fibrosis with the dysphagia of cardiospasm,^{30, 31, 32} the present survey was undertaken in order to examine the possibility that the pulmonary changes in scleroderma are secondary to aspiration. If aspiration were the chief cause of the pulmonary changes in scleroderma, esophageal lesions would be present in *all cases* with pulmonary findings.

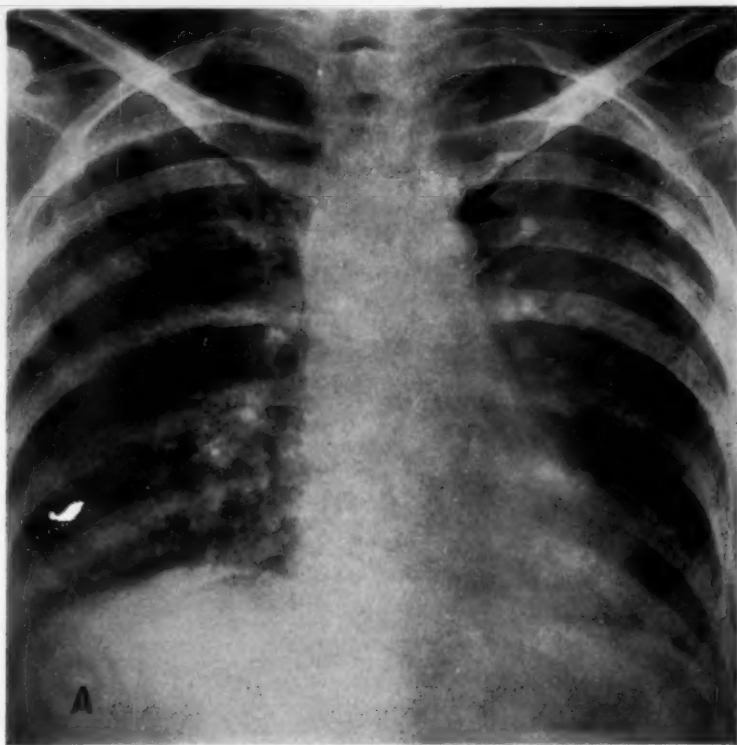


FIG. 3A. Case 45. Generalized and patchy mottling throughout lungs.

In the series from the literature (table 1), 56 per cent had esophageal involvement. In our own cases (table 2), 69 per cent had esophageal involvement. This is in close agreement with the 45 per cent and 59 per cent reported in unselected series.^{27, 28} In fact, in several cases at post mortem no esophageal changes were found. Unlike the pulmonary fibrosis seen in cardiospasm, the lung lesions in scleroderma in one-half of the cases showed characteristic cystic changes. Thus, while aspiration pneumonia and sub-

sequent pulmonary fibrosis may conceivably occur, they are not the primary factors in the pulmonary disease.

SUMMARY AND CONCLUSION

The pulmonary changes in scleroderma have been studied in 57 cases. Clinically, dyspnea was the most common complaint. Radiologically, the picture is that of fibrosis with occasional cyst formation, mostly confined to

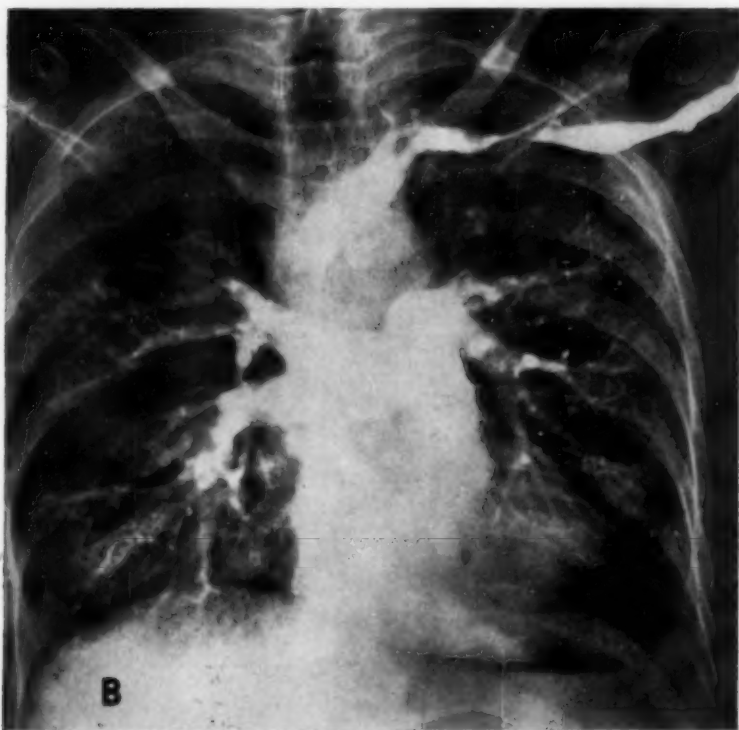


FIG. 3B. Case 45. Angiocardiogram shows slight enlargement of pulmonary artery and branches associated with pulmonary hypertension. Abnormal peripheral vascular pattern is present, particularly right upper lobe.

the bases. Functional studies indicate that there is a barrier at the alveolar membrane. Cor pulmonale is a late change in the progressive fibrosis. The pathologic changes consist of fibrosis; in one-half of the cases cystic bronchiolar hyperplasia is demonstrated. Esophageal lesions are found in only 56 per cent (table 1) and 69 per cent (table 2), thus eliminating aspiration pneumonia as the primary cause of the pulmonary disease.

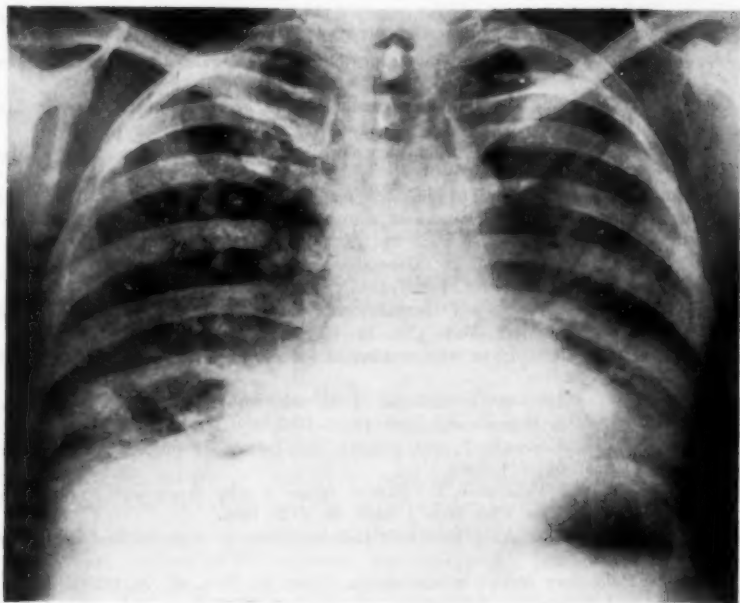


FIG. 4. Case 53. Enlarged heart with prominent pulmonary artery and pulmonary congestion in a patient who died with cor pulmonale. Lung fields show diffuse fine reticulonodular densities.

The incidence of pulmonary involvement is probably greater than is appreciated. Sixteen cases were found at this center among 79 cases of scleroderma, an incidence of 20 per cent.

ADDENDUM

Since this paper was submitted for publication, Shuford et al.³¹ have reported five patients with pulmonary changes and scleroderma; a sixth patient whose initial roentgenogram was clear died because of the development of pulmonary edema and at autopsy had connective tissue proliferation of the alveolar walls. Five additional cases of pulmonary involvement in scleroderma are abstracted in *The Year Book of Radiology* (*The Year Book Publishers, Inc., Chicago, 1953, p. 173*). These cases were reported by Deenstra, H., and Jansen, L. H.: *Nederl. tijdschr. geneesk* **96**: 3073-3078 (Dec. 6) 1952.

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**SARCOIDOSIS—HEPATIC INVOLVEMENT:
PRESENTATION OF A CASE WITH FATAL LIVER
INVOLVEMENT, INCLUDING AUTOPSY FIND-
INGS AND REVIEW OF THE EVIDENCE
FOR SARCOID INVOLVEMENT OF
THE LIVER AS FOUND IN THE
LITERATURE***

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INTRODUCTION

REPORTS of sarcoidosis of the liver are infrequent in the literature, although within the past five years more attention has been given to this aspect of the disease, and since the time of the conception of this study several excellent treatises on the subject have appeared in the literature.

A case of such extensive liver involvement as to be the direct cause of death was under the observation of the authors for the three years prior to death. To the best of the authors' knowledge this is the first report of its kind in the literature.

It is the purpose of this paper to present this case with the biopsy and autopsy findings and to review briefly the history of sarcoidosis, the problem of etiology and the latest concepts of treatment. Detailed study of the clinicopathologic features of the disease will be presented with particular emphasis on the liver, as to both clinical and histopathologic involvement. In the preparation of this study, 656 cases of sarcoidosis reported in the literature were selected for review of the clinical aspects of the disease, 710 reported cases surveyed for evidence of liver involvement from the clinical standpoint, 1,106 instances of liver biopsy reviewed for histopathologic liver involvement, and, finally, 138 autopsy protocols analyzed in an effort to learn more about the frequency, extent and type of involvement of the liver in this disease.

CASE REPORT

A 51 year old white housewife was first seen December 9, 1946. She complained of gradually increasing ease of fatigability on mild exertion for a period of 24 months, a 40 pound weight loss over a period of 20 months, a mildly itchy skin eruption of the forearms and upper back for seven months, and loss of appetite and gradually deepening jaundice for three weeks.

Past History: The patient stated that she had had typhoid fever without complications or sequelae at the age of five years. She had had the usual childhood

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diseases, but no scarlet fever, rheumatic fever or diphtheria. She had had one bout of urticaria a number of years previously, but did not know the offending allergen. She had enjoyed good health until 1924, when she first noted a swelling at the base of the neck on the right side. In May of that year a benign thyroid cyst was removed. Her physical examination and routine laboratory findings during this hospital admission were all within normal limits. She had an uneventful recovery, and felt well until 1944, when a uterine prolapse became annoying and she began to complain of ease of fatigability on mild exertion. In 1946 a vaginal hysterectomy and perineorrhaphy were done. At this time her physical and laboratory findings were also within normal limits. The pathologic report revealed an atrophic uterus, and a small, non-malignant polyp was found within the cervical canal. Her convalescence was uneventful.

Family History: No history of familial disease was elicited.

System Review: Save for the facts brought out above and in her present illness, the review was noncontributory to her medical history. She had had no pregnancies.

Social History and Habits: The patient had never used alcohol or tobacco in any form. Her diet had been adequate. She had used no unusual drugs and had not come into contact with any toxic substances. She had not been outside the continental bounds of North America. Her family and social background was a congenial and stable one. Sleep, recreation and exercise were adequate.

Present Illness: Just prior to her vaginal hysterectomy in 1946 the patient had begun to show early symptoms of menopausal disturbance. These continued following her operation, but in addition she noted that climbing one flight of stairs caused her considerable fatigue. One month later she noted for the first time areas of dull red, flat-topped, shiny, discrete itchy papules which appeared on the volar surfaces of both forearms, and later on the upper back. She also began to lose weight at an increasing rate, so that by December of that year her weight had dropped from 185 pounds to 141 pounds (a loss of 44 pounds in seven months).

Physical Examination: Patient appeared to represent her chronologic age of 51 years. She obviously had lost considerable weight. She had prominent xanthelasma palpebrarum and an icteric tint to the skin and sclerae. Dull red papules were seen over the extensor and flexor surfaces of both forearms, and in the interscapular area of the back. These lesions were discrete, averaged 3 mm. in diameter, and were raised above the surface of the skin about 1 to 2 mm. The rest of her skin was extremely dry and mildly ichthyotic. Her height was 69 inches; weight, 141 pounds; temperature, 98.6° F. Pulse was 80, full and regular; blood pressure, 140/95 mm. of Hg. No murmurs were heard on auscultation of the heart, and there was no enlargement of the heart by percussion of the cardiac borders of dullness. The liver was enlarged and extended 8 cm. below the right costal border; it was firm and non-tender, and had a rounded edge. The spleen was enlarged and extended 4 cm. below the left costal border.

On pelvic examination no uterus was palpated; otherwise the examination was negative. Rectal, neurologic and orthopedic examinations were negative. There was no peripheral lymph node enlargement. The tonsils were atrophic.

A summary of the laboratory findings is found in table 1.

Intracutaneous PPD tuberculin tests (first and second strengths) were both negative. Roentgenograms of the bones of the hands showed a few bone islands in the distal phalanges of the third and fourth fingers on the right, and of the second, third, fourth and fifth fingers on the left, but no cystic areas were seen. Chest films (figure 1) revealed an increase in the width of the hilar shadows due to enlarged mediastinal glands, and some infiltration in the left lower lung field. Flat films of the abdomen showed only an enlarged liver and spleen. An aspiration biopsy of the sternal bone marrow failed to demonstrate any abnormalities. The biopsy of one of

the skin nodules in the interscapular area (figure 2) revealed the typical granulomatous tubercles characteristic of sarcoidosis, and it was upon this conclusive evidence that the diagnosis was established.

The patient was kept on a high protein, high carbohydrate diet with vitamin supplements, and in addition was given Intraheptol liver extract intravenously three

TABLE I
Summary of Laboratory Findings

Test	December, 1946– January, 1947	September, 1948	June, 1949
Cephalin cholesterol flocculation	2 + (24 hrs.)	1 + (24 hrs.)	3 + (24 hrs.)
B.S.P. Retention—after 5 min. after 30 min.	50% 0	70% 35%	
Icterus index		50	84
Prothrombin time % of control	17.5 secs. 80%	20.0 secs. 82%	15.5 secs. 80%
Serum protein	6.7 gm.	5.9 gm.	7.0 gm.
albumin	3.3	2.1	2.7
globulin	3.4	3.8	4.3
A/G ratio	0.97	0.6	0.6
Serum cholesterol			329 mg. %
Serum cholesterol esters			270 mg. %
Blood nonprotein nitrogen	30 mg. %	27 mg. %	38 mg. %
P.S.P. renal function—1 hr. 2 hrs. Total %	45% 27% 72%		
Hemoglobin	14.0 gm.	10.0 gm.	13.5 gm.
Red cell count	4,100,000	3,600,000	4,400,000
White cell count	4,000	5,700	4,240
Abnormalities in hemogram	6% eosinophils	3% eosinophils	None
Blood Hinton	Negative	Negative	Negative
Sedimentation rate (Westergren)	90 mm./1 hr.		
Abnormalities in urine	bile—2 + 30–40 WBC/10 HPF	bile—4 + 250 WBC/10 HPF numerous rbc's	bile—4 + albumin—2 + occasional rbc's and finely granular casts

times a week. She gained appetite but failed to gain weight, although she was on a program of enforced rest (but not confined to bed).

Six months later the patient complained of pain in the right side of the neck and in the left lower chest on deep inspiration. She had had a mild upper respiratory infection the week before. Examination of the patient revealed the mucous mem-

branes to be pale. The degree of icterus was less. Fine crepitant râles were heard at both lung bases, and a friction rub was heard at the left lung base in the anterior axillary line. The liver had descended to the level of the umbilicus and was tender, and the spleen was larger than at the time of her first examination. Laboratory findings remained essentially the same, save for the fact that there was less bile in the urine, and the eosinophil count had dropped to 3 per cent and the hemoglobin to 11.5 gm.

Two months later the patient was admitted to the hospital because of substernal and precordial pain, progressive weakness and increasing fatigue and dyspnea on

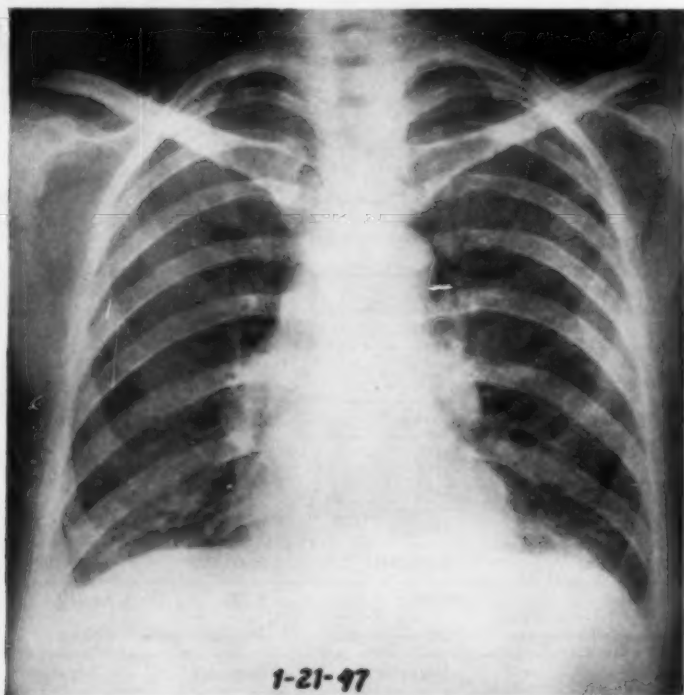


Fig. 1. Chest film of January 21, 1947, showing increase in width of the hilar areas due to enlarged mediastinal glands and some infiltration in the left lower lung field.

exertion. For about two weeks she had also noted some irregularity of the heart beat. Examination of the patient revealed not only the findings as noted above but also a Grade II systolic murmur, heard loudest over the apex and not transmitted. The heart sounds were less distinct than on previous examination. Blood pressure was 130/80 mm. of Hg. No peripheral lymph node enlargement was noted. Laboratory findings were essentially unchanged save for a decrease in the white cell count to 2,800. Chest x-ray showed an increase in the width of the hilar shadows and more parenchymal infiltration in the left lower lobe. The electrocardiogram revealed a number of premature ventricular systoles and low voltage, and slurred QRS com-

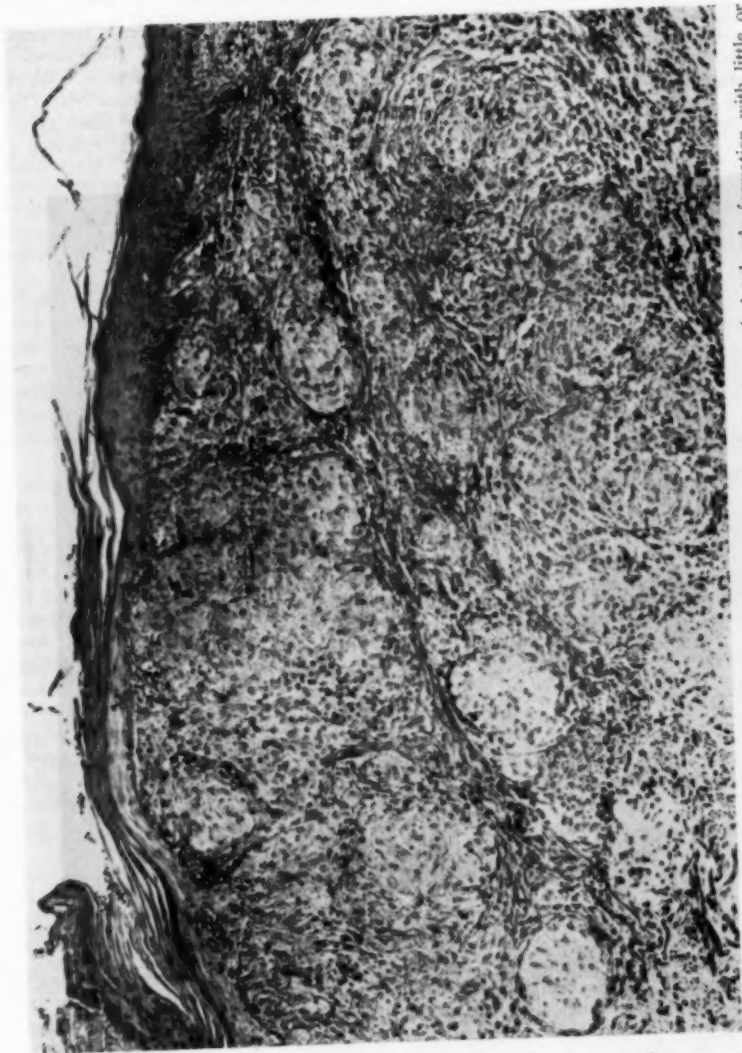


FIG. 2. Photomicrograph of skin biopsy of January 24, 1947, showing typical tubercle formation with little or no central necrosis, a few giant cells and some lymphocytic infiltration near the periphery. It was this skin biopsy which definitely established the diagnosis of sarcoidosis in this case.

plexes in all of the standard limb leads, but no significant abnormalities in the precordial leads. The patient was discharged to her home and advised to include a protein hydrolysate in her diet.

Eight months later the patient was re-admitted to the hospital, deeply jaundiced and showing marked weight loss. The entire body was covered with sarcoid papules. She no longer complained of any pain in the chest or in the neck. Râles persisted at the lung bases, although the friction rub had entirely disappeared. The systolic murmur was of much less intensity at the apex, a finding which, when taken into account along with the reduced blood pressure of 100/80 mm. of Hg, reflected a

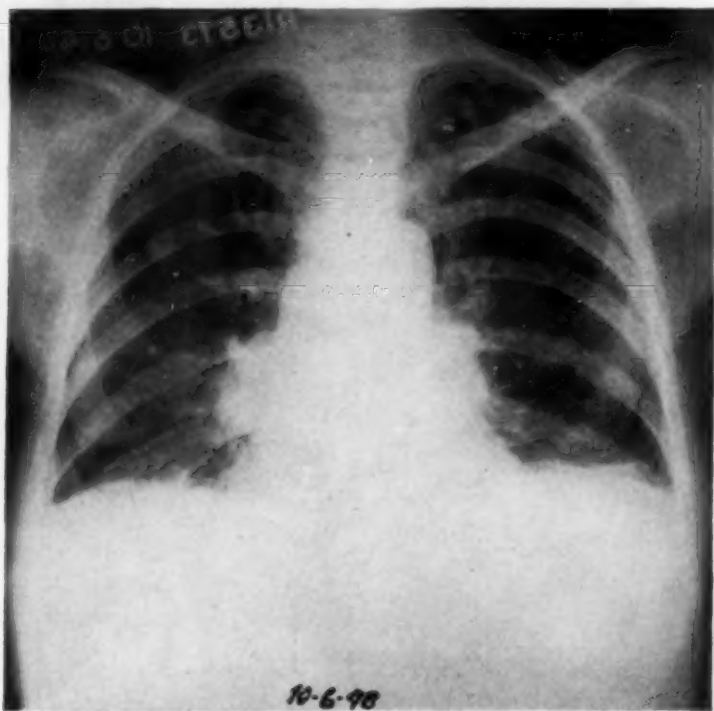


FIG. 3. Chest film of October 6, 1948.

weakening myocardium. The liver had shrunk to within 6 cm. of the right costal margin, and the palpable portion was hard and nontender. The spleen was barely palpable. Moderate ascites was now present, and a complete vaginal wall prolapse was noted when the patient stood erect. There was no edema of the lower extremities.

Over the course of the next five months the patient's condition continued to deteriorate. Weakness and dyspnea on the slightest exertion became more marked. She complained of frequency of urination, of flatulence and gaseous eructations. The stools were clay-colored and often watery. The râles heard over both sides of the chest now extended up to the angles of the scapulae. Ascites was increased, the

vaginal vault eversion more accentuated, and a rosette of engorged external hemorrhoids appeared. Two plus pitting edema of the feet extended part way up the legs. On October 4, 1948, a liver biopsy was done with some difficulty, due to the extremely firm, rubbery resistance of the liver. An unsatisfactory specimen was obtained. The icterus index was higher, the A/G ratio more pronouncedly reversed, and there was 35 per cent bromsulfalein retention after 45 minutes. Chest film (figure 3) showed more extensive involvement of the mediastinal lymph nodes.

The patient was placed on a 0.5 gm. daily maximal intake of sodium, and the fluids were restricted to 1,500 c.c. as an additional precaution in case the patient was unable properly to restrict her sodium intake; in addition, she was given 1.0 gm. ammonium chloride three times a day after meals, with Theophylline-Salysrgan injections intramuscularly every second day. The liver extract and vitamins were continued as before.

In two weeks' time the patient had lost all ascites and ankle edema, had gained 10 pounds in weight, and appeared and felt a great deal better; and the icterus of skin and sclerae began to diminish. Over the next three months the skin lesions became much less prominent, the râles at the lung bases disappeared, the heart sounds improved and the systolic murmur could no longer be heard. The electrocardiogram showed little change from the previous tracing, save for a diminution in the voltage of T_1 and T_2 . Liver and spleen remained about the same size. At this time the patient's weight was 140 pounds and blood pressure 120/80 mm. of Hg.

This period of improvement, however, was of short duration, and during the next eight months the ascites reappeared, the jaundice became quite pronounced, the weakness and dyspnea on exertion quite marked, and there was incontinence of urine. The sarcoid papules of the skin, however, had continued to fade and diminish in size, and in many places were almost imperceptible. With the ascitic fluid accumulation the patient's weight had gone up to 159 pounds, and an umbilical hernia had developed in addition to the vaginal vault eversion. Her blood pressure was 95/60 mm. of Hg, the heart sounds were of fair quality, and no murmurs were heard. Râles and dullness to percussion over both lower lung fields posteriorly were noted. Cervical, axillary and inguinal lymph nodes now became enlarged for the first time. The ankles and lower legs showed a 3 plus pitting edema. After the removal of 6 quarts of ascitic fluid by abdominal paracentesis the liver edge was felt at the level of the umbilicus, and was sharp and nontender. The spleen extended 7 cm. below the left costal margin.

Another intracutaneous tuberculin test, using 0.1 mg. O.T., was negative; the ascitic fluid cultures revealed no acid-fast organisms, and no abnormal cells or bacteria were seen on smears.

The patient continued to seep a great deal of fluid through the paracentesis wound for the next three days, and with her first mercurial diuresis in three weeks she lost 3,120 c.c. of urine in 36 hours. Three transfusions of 500 c.c. whole blood each and 40 c.c. of concentrated human albumin were given. Within 72 hours after these procedures had been completed her weight had dropped from 159 to 128 pounds. The patient was given 300,000 units of procaine penicillin G every 12 hours during the next 10 days. At the time of her discharge from the hospital (July 6, 1949), a rough rumbling Grade III systolic murmur was heard just to the left of the midclavicular line in the fourth interspace.

Paracenteses had to be performed at home on an average of twice a week for the next month. At this time the patient had an emergency admission to the hospital for the removal of a spicule of beef bone which had become lodged in the upper third of the esophagus while she was eating her noonday meal. This was removed without incident under Pontocaine and Pentothal anesthesia. The patient was noted to have a great deal of spontaneous bleeding from the gums; this responded well to the paren-

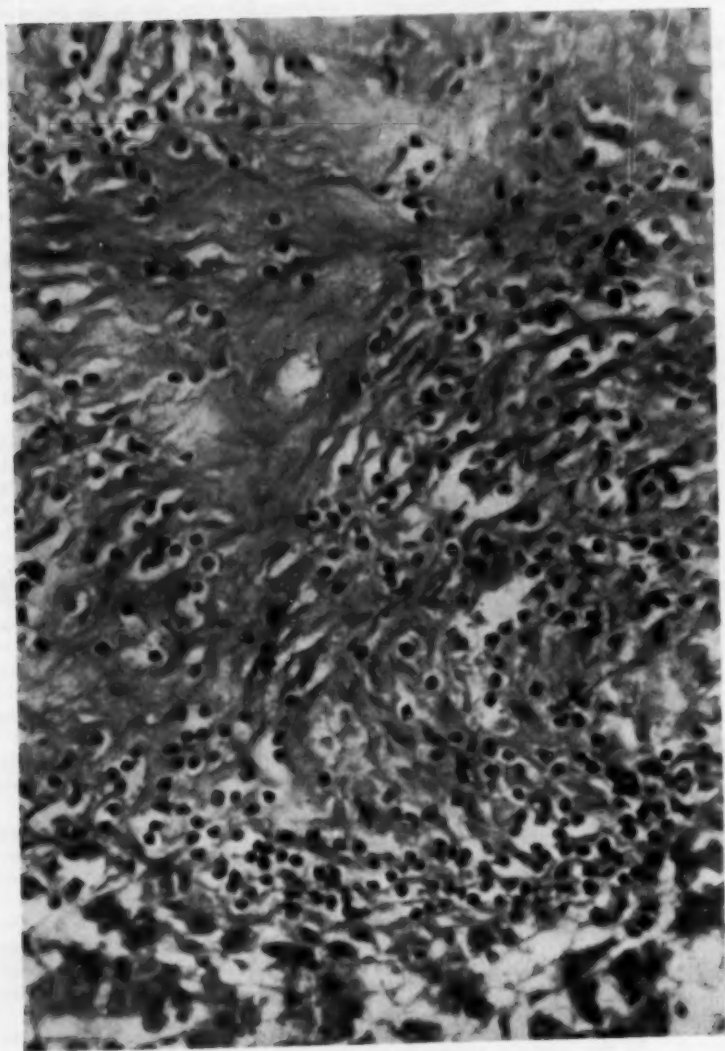


FIG. 4. Photomicrograph of section of spleen (autopsy).

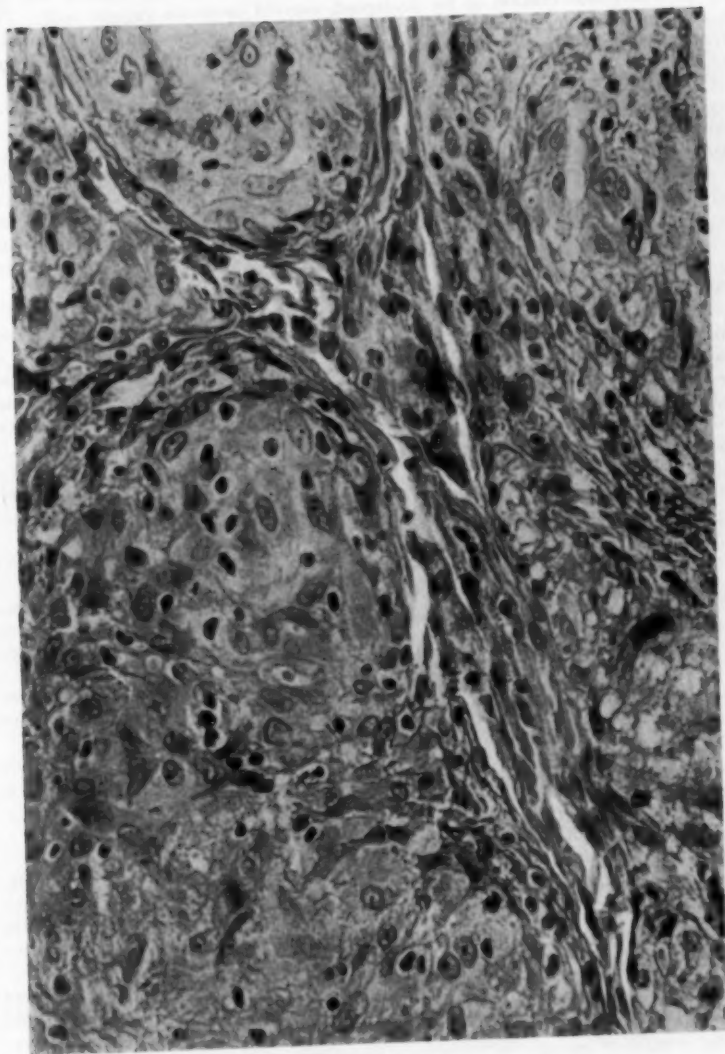


FIG. 5. Photomicrograph of section of lymph node (autopsy).

teral administration of vitamin K. The liver had receded to within 2 cm. of the right costal margin, and the spleen could just barely be felt. The systolic murmur was unchanged. There was erosion of the prolapsed, everted posterior vaginal wall. The urine continued to show more bile and albumin and many coarse and finely granular casts, and for the first time a few hyaline casts appeared. The patient was discharged to her home.

A month later the patient had her seventh and last hospital admission for this illness. She had developed fever, rigors, malaise and severe anorexia. On admission her temperature was 101° F.; pulse, 120 and regular; respirations, 36; blood pressure, 65/40 mm. of Hg. Heart sounds were very faint, and dullness and râles were found over the lower two thirds of both lung fields posteriorly. The patient became extremely cyanotic shortly after admission, complained of sudden and intractable left upper quadrant abdominal pain, vomited a moderate amount of undigested food, and in spite of oxygen and other supportive therapy died at 6:15 p.m., just five hours after admission.

An autopsy was performed approximately 13 hours after death.

Autopsy Findings: The features of interest were the multiple linear, punctate and diffuse scars in the superficial skin of the neck, chest and abdomen, the 8,000 c.c. of gray-green ascitic fluid, generalized lymphadenopathy and a large liver and spleen. There were also found a terminal pneumonitis and bilateral hydrothorax, a terminal endocarditis involving the mitral valve, and an extensive vaginal prolapse with ulceration of the mucosa which, on examination, had not perforated the vaginal wall.

The liver weighed 3,258 gm. and was irregularly nodular and of firm consistency. On section the cut surfaces were a dull gray-green, with irregularly distributed islands of yellowish pink tissue interspersed throughout. The gall-bladder and bile ducts were grossly normal.

The spleen was lobulated and soft, and the capsule wrinkled. The cut surfaces were chocolate-red in color.

The sternal, anterior and posterior mediastinal and tracheobronchial lymph nodes were discrete, of rubbery consistency and enlarged to an average diameter of 4 cm. The cut surfaces of these nodes were mottled gray and had a greasy appearance. Some showed foci of calcification.

The right lung weighed 745 gm., the left 665 gm., with no scarring or demonstrable atelectasis. Crepitation was diminished. The cut surfaces were dark red and showed moderate edema.

The pancreas and kidneys were not remarkable. The left ureter was slightly dilated, the cause of which was not explained from the gross dissection. There was no evidence of obstruction in the course of this ureter.

The internal genitalia had been removed at a previous operation.

The bone marrow was grossly normal.

Microscopic examination of the tissues showed lesions present in the skin, lung, liver, spleen and lymph nodes having the characteristic histologic changes of sarcoid. These lesions were distinguished by the presence of tubercles within which were found giant cells, a moderate degree of infiltration of lymphocytes and mononuclear cells, and no evidence of caseous necrosis.

The lesions in the liver were diffuse and varied in size, and were more prevalent in the interlobular spaces. The connective tissue had a hyalinized appearance, and the fibers adjacent to the tubercle stained slightly basophilic. Throughout the liver there was a marked increase in connective tissue, and in many of the portal spaces bile duct proliferation was marked. Bile stasis was diffuse, involving the intercanalicular and larger bile radicles. The hepatic cells in many instances showed loss of cytoplasm. Vacuoles were present which probably represented fat that had been removed in the fixing. Sections stained for fat gave a positive reaction and showed

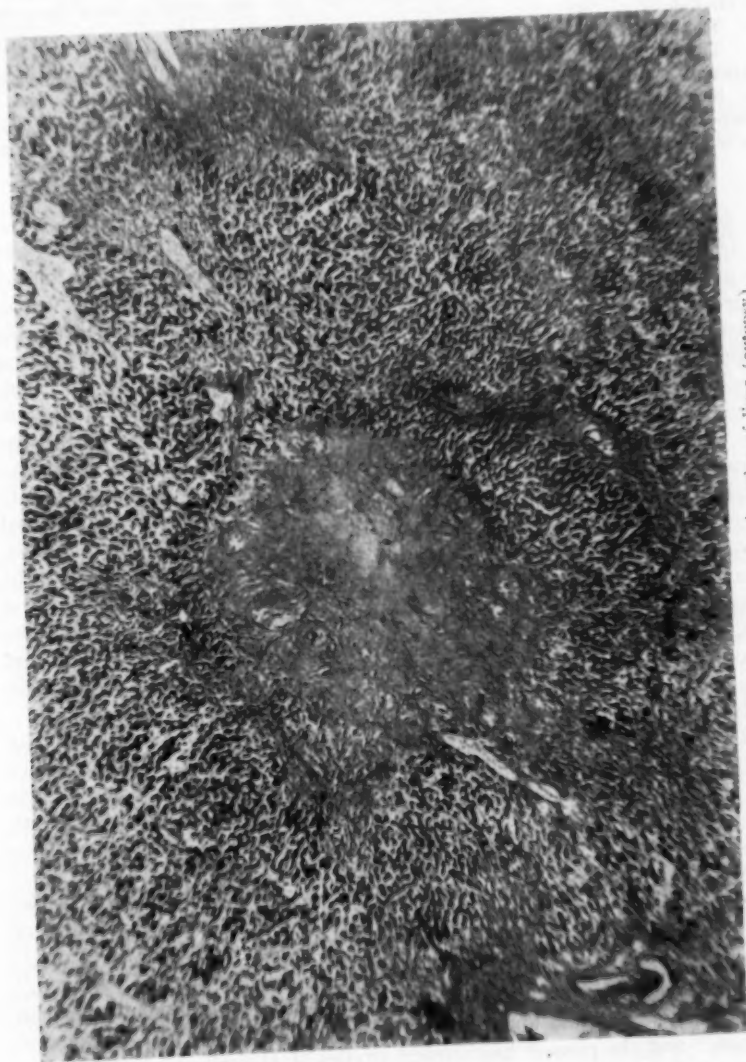


FIG. 6. Photomicrograph of section of liver (autopsy).

a diffuse distribution with no predisposition for any particular zone. Sections stained for acid-fast organisms revealed none to be present. Hyaline necrosis was not found. The histopathology was that of a cirrhosis which was interpreted as being the result of sarcoidosis.

The pneumonitis was of a lobular type and not specific in character.

The endocarditis was of recent origin, and was interpreted as a complication of a terminal sepsis.

Sarcoid lesions were not found in the bone marrow, adrenals or kidneys. The diagnosis was that of sarcoidosis complicated by hepatic insufficiency and overwhelming terminal sepsis.

HISTORICAL NOTES

Hutchinson^{1,2} first described the skin lesions of sarcoidosis in 1875, and in 1898 gave to the disease the name "Mortimer's malady" (after one of his patients). Because of the resemblance of the skin manifestations to the efflorescences of chilblains, or "chilblain lupus," Besnier³ in 1889 gave the name of "lupus pernio" to the disease. Then in 1899 Boeck⁴ gave the first authentic and accurate pathologic picture of the disease, and called it "multiple benign sarcoid of the skin." Later he changed the terminology to "benign miliary lupoid." From that time until about 15 years ago the disease was most commonly known as Boeck's sarcoid. In the European literature, however, the name of Besnier-Boeck-Schaumann's disease is still widely used. According to Kissmeyer,⁵ Kienböck in 1902 first described the cystic bone changes, but thought they were a manifestation of syphilis. It was not until 1920 that Jüngling⁶ incorporated the bone changes into the pathologic picture of the disease. Kissmeyer⁵ in 1932 was one of the first to recognize the fact that the liver and other digestive organs, as well as the skin, bones and lymph glands, were involved in this disease. Kutzinsky and Bittorf⁷ described the pulmonary lesions and correlated them with the skin manifestations.

In 1917 Schaumann^{8,9,10} began integrating histologically and accurately the lesions in the skin and lymph nodes. He showed that the sarcoid of Boeck and lupus pernio of Besnier were histologically the same disease. He also reported the generalized systemic characteristics of the disease with predilection for lymphoid tissue and gave the name of "lymphogranulomatosis benigna" to this complex picture.

In the last 15 years much of the confusion of the past has been dispelled by the outstanding comprehensive and critical analyses of large numbers of cases of this disease reported in the literature by Pinner,¹¹ Longcope,¹² Thomas,¹³ Reisner,¹⁴ Rubin and Pinner,¹⁵ McCort, Wood et al.,¹⁶ Freiman,¹⁷ Ustvedt,¹⁸ Ricker and Clark,¹⁹ Vivas, Smith et al.,²⁰ Hunnicutt, Nushan et al.,²¹ Riley,²² Klatskin and Yesner,²³ Michael, Cole et al.,²⁴ Longcope and Freiman,²⁵ and the pioneer biochemical studies of Harrell and Fisher²⁶ and of Harrell.²⁷ Today the term "sarcoidosis" is almost universally accepted throughout the world, and this disease is beginning to come into focus as a distinct entity. Our knowledge, however, is infinitesimal compared to our

ignorance in regard to many aspects of sarcoidosis. The key to the riddle of etiology, the answers to the questions concerning the mechanism of the formation of the tubercles and tissue specificity and selectivity whereby tubercle growth is accepted or rejected, and the solution to the problems of specific treatment and prevention, all lie in the future.

Many excellent brief summaries of the disease have been published in the past four years, and special reference is made to those of Curtis and Grekin,²⁸ Wintrobe,²⁹ Middleton³⁰ and Sacks.³¹

CLINICOPATHOLOGIC FEATURES

As indicated above, the etiology of sarcoidosis is still unknown. There have been many theories to explain its causation; one of the most popular, especially in the Scandinavian countries, is that sarcoidosis is an aberrant form of tuberculosis. Pinner¹¹ and Rubin and Pinner¹⁵ present much evidence to support this theory, and one is certainly impressed with the high incidence of tuberculosis found either concomitantly with or following a healing or remission phase of this disease. Longcope and Freiman²⁵ and Sacks³¹ estimate that 15 to 25 per cent of all cases of sarcoidosis are associated with tuberculosis at one time or another. In order to explain the high incidence of negative tuberculin tests in this disease, some feel that sarcoidosis is a form of tuberculosis in an anergic phase. However, no culture or immunologic technic has yet been devised which can establish any definite relationship between the two diseases. The healing sarcoid tubercle retains its original size and shape, although it may be completely hyalinized, while the acid-fast lesion rapidly loses its original configuration. The fibrous reticulum, fairly characteristic of the sarcoid tubercle, is rarely if ever seen in its tuberculous counterpart. Tuberculosis of the adrenal gland is not at all uncommon, yet Longcope and Freiman²⁵ and the authors could find record of only one instance in which this gland was invaded by the sarcoid process. There are at least 23 proved cases of sarcoidosis of the heart (for references see table 7), with about one third of these having the sarcoid involvement listed as the immediate cause of death. Tuberculous myocarditis is generally conceded to be quite rare. A review of more than 137 autopsy reports showed the spleen to be involved in about 49 per cent of the cases where sarcoidosis was an established diagnosis. It is estimated that the spleen is involved in well over 85 per cent of the patients with miliary tuberculosis. It is also of interest to note that VanBuchen,³² who did puncture biopsies of the livers of 14 patients with sarcoidosis, found the typical tubercles in 11 cases, while biopsies done on the livers of nine patients with exudative pulmonary tuberculosis contained no evidence of disease. Furthermore, Pare, Freiman and McCort,³³ who are studying 25 patients with sarcoidosis at the Massachusetts General Hospital, report no tuberculosis developing in any of these patients after follow-up periods ranging from five to 28 years.

The problem of etiology, then, is still quite unsettled. Some investigators consider yeast as a possible factor, others feel that sarcoidosis is a collagen disease, while still others feel that it is one of the lymphomatous group.

As one reviews one's own experience and the literature it becomes obvious that sarcoidosis is first manifest in the young adult, usually the 20-to-40 year age group. Because of the early interest and pioneer investigative work done in connection with this disease in the Scandinavian countries, one is apt to get the impression that the incidence of sarcoidosis in those countries is particularly high, but as interest in the disease has spread and routine chest x-ray studies become more of an acknowledged valuable preventive medical procedure in an increasing number of nations, reports have been, and still are, appearing in the literature indicating the worldwide extent of sarcoidosis.

It is difficult to ascertain with any degree of accuracy the incidence of sarcoidosis in the general population. Schönholzer,²⁴ after examining the recruiting records of 500,000 young men inducted into the Swiss Army, finds that 115 cases with a provisional diagnosis of sarcoidosis were set aside after routine chest fluoroscopy, but that only 67 were finally considered definitely to have the disease, giving an incidence rate of 13 per 100,000. More recently Michael, Cole et al.²⁴ have undertaken an epidemiologic study of 226 cases of substantiated sarcoidosis found among the 8,288,000 inductees into the U. S. Armed Forces. This is an incidence of 2.73/100,000. These same investigators also found that 88 per cent of these cases came from the southern United States and that southern-born Negroes with the disease had a higher incidence when compared to northern-born Negroes, in the ratio of 24.63 to 1.58 (per 100,000). They inject the thought-provoking speculation that geographic epidemiologic factors may play a more important part than racial ones in the predisposition to this disease.

In analyzing the 571 cases reported by McCort, Wood et al.,¹⁶ Ricker and Clark,¹⁹ Hunnicutt, Nushan and Miller,²¹ Riley,²² Longcope and Freiman²⁵ and Dickie and Middleton,²⁵ we find 454 of the cases were in Negroes (or 79.5 per cent of the 571 cases reported). The extremes in this series were 9.1 per cent of 11 cases of Dickie and Middleton,²⁵ and 94.4 per cent of 300 cases of Ricker and Clark.¹⁹ Omitting for obvious reasons the cases reported from Army hospitals by McCort, Wood et al.¹⁶ and Ricker and Clark,¹⁹ we find the average mean age of 101 cases to be 30.25 years; also that 121 of 205 cases (or 59 per cent) were in females.

As Longcope and Freiman²⁵ point out, the disease is definitely identified earlier in the Negro. Whether the disease has an earlier onset in the Negro, or whether it progresses more rapidly and becomes symptomatic sooner, is a question open to speculation; but it is apparent that the disease is most often diagnosed in the Negro at around 25 years of age, as contrasted with around 35 or over in white patients. Extremes of age from three months to 87 years have been reported.

The onset of the disease is insidious and the symptoms are protean, as might be expected in view of the widespread distribution of the sarcoid lesions through the body. Table 2 lists the symptoms most commonly found, in the order of their frequency.

The typical sarcoid lesion varies little with the tissue in which it is found. It consists of a single tubercle or, less frequently, a mass of tubercles composed of large, pale epithelioid cells, with few infiltrating or surrounding "collar" lymphocytes. These granulomas tend to cluster about small blood vessels or lymphatics, and may in large numbers diffusely replace an involved tissue section or an entire organ such as the spleen. However, the individual granulomas do not tend to become confluent. A fine fibrous reticulum penetrates throughout the entire granulomatous lesion. Very few neutro-

TABLE II

Symptoms of Sarcoidosis Listed in Order of Frequency

(As found by three groups of investigators studying patients from U. S. Army hospitals, New England, the South and the Eastern Seaboard.)

McCort, Wood et al. ¹⁴ (28 cases from U. S. Army hospitals)	Hunnicut, Nushan et al. ²¹ (38 cases from the South)	Longcope and Freiman ²⁵ (142 cases from New England and Eastern Seaboard)
Dyspnea	Weakness	Ocular
Ocular	Joint and muscle pains	Cough
Cough	Anorexia	Fatigue
Chest pain	Loss of weight	Malaise
Loss of weight	Ocular	Loss of weight
No symptoms	Fever	Dyspnea
Weakness	Cough	Skin eruption
Fever	Dyspnea	Lymph node swelling
Anorexia	Lymph node swelling	Abdominal pain
Nausea	Skin eruption	No symptoms
Vomiting	Tachycardia	Anorexia
Skin eruption	Hemoptysis	Night sweats
	Swelling of joints	Parotid swelling
	Vertigo	Fever
	Nausea and vomiting	Hoarseness
		Abdominal mass
		Chest pain
		Nausea and vomiting
		Jaundice—1 case
Total—208 cases		

phils or eosinophils are seen, and usually multinucleated giant cells (which in about 30 per cent of the cases contain one or another of the three types of inclusion bodies as described by Longcope and Freiman²⁵) are seen around a central area which only rarely shows any appreciable degree of necrosis.

Almost every organ and tissue in the body have been shown at one time or another to be involved. The granulomas may develop and remain unchanged for months or years; or may completely resolve, leaving no trace; or may go on to diffuse and extensive fibrosis, with collagen or hyalin formation developing and progressing centripetally from the periphery.

The results of the clinical investigation of eight groups of workers studying 607 cases of sarcoidosis in recent years will be presented here to show the extent of organ involvement in this disease (table 3).

TABLE III
Percentage of Clinical Involvement of Various Organs

Investigators	No. of Cases	Lymph Nodes	Lungs	Liver	Spleen	Bones	Skin	Ocular and/or Parotid
Klatskin and Yesner ²³	15	11/15 IT 7/15 P	6/15	11/15 (biopsy)	6/15	0/15	1/15	2/15
Longcope and Freiman ²⁴	142	128/142 LNS 34/52 IT 29/52 P	100/142	35/142	44/142	19/100	49/142	60/124
McCort, Wood et al. ¹⁰	28	28/28 IT 26/28 P	15/28	—	3/28	6/27	2/28	11/28
Reisner ¹⁴	35	30/35 IT 35/35 P	33/35	6/35	8/35	9/35	14/35	—
Ricker and Clark ¹⁹	300	249/300 LNS *76.0% IT	*36.0%	26/300	24/300	*36.0%	63/300	26/300
Riley ²⁵	52	52/52 LNS	45/52	19/52	21/52	7/52	13/52	16/52
Thomas ¹³	15	14/15 LNS	14/15	6/15	6/15	—	14/15	—
Vivas, Smith and Jacobs ²⁶	20	20/20 IT 19/20 P	20/20	5/20	6/20	3/20	—	—
Total Cases	607	443/509 LNS 123/150 IT 116/150 P	233/307	108/579	118/607	44/249	156/587	115/519
Average Percentage Involvement (clinical)		87.0% LNS 82.0% IT 77.5% P	76.0%	18.7%	19.4%	17.7%	26.6%	22.2%
Average Percentage Involvement (after analysis of 138 autopsies)		77.7% LNS	77.0%	66.5%	49.5%	16.2%	16.2%	6.0%

Note: Numerators indicate instances of positive involvement; denominators indicate total number cases examined for this involvement.

* Figures expressed in percentages opposite the investigators indicate percentages reported by the authors but are not computed in the final percentages as inadequate data for the above analysis are presented.

Unless otherwise stated, the criteria for liver involvement are based on hepatomegaly and/or laboratory data indicating liver damage.

LNS—location not specified; P—peripheral; IT—intrathoracic.

Additional data from autopsy analysis—

Cardiac.....	19.6%
Central nervous system.....	7.7%
Genitourinary.....	10.2%
Gastrointestinal.....	6.0%
Endocrine.....	6.0%

Laboratory Studies: The outstanding significant abnormalities in the field of laboratory investigation are of course to be found in the serum proteins. As early as 1939 Harrell and Fisher,²⁸ and Harrell²⁷ in 1940, called attention to the comparatively high incidence in this disease of hyper-

globulinemia, with relatively little elevation in the total serum protein. This aspect of sarcoidosis will be dealt with in more detail under the section on hepatic involvement.

Elevation of the serum calcium with little change in the phosphorus values has also attracted interest in recent years. Harrell and Fisher²⁶ report five of their 11 cases with calcium levels over 11 mg. per cent; McCort, Wood et al.¹⁶ found the calcium over 10.5 mg. per cent in 10 of their 16 cases, and Longcope and Freiman²⁵ compare 23 cases in the Johns Hopkins series, in which six were found to have a serum calcium over 11 mg. per cent, with five cases of the 21 reported in the Massachusetts General series which had over 12 mg. per cent. Most investigators agree that there is no correlation between the calcium levels, the globulin fraction, the alkaline phosphatase and/or the degree of bone involvement. Recent observers have found the hypercalcemia to be associated with renal calculi, renal insufficiency and diffuse calcinosis. Four cases of elevated serum calcium are reported by Phillips²⁶ and Shulman, Shoenrich et al.²⁷ in which ACTH or cortisone was used with good effect to correct the calcium levels. However, Phillips²⁶ noted little improvement in the function of the already impaired kidney when using these steroid hormones. There may have been a prophylactic effect in the cases of the second group of investigators, as these cases were treated before any serious degree of kidney impairment had taken place.

For several years an elevated serum alkaline phosphatase was considered by some to be an indication of activity of sarcoidosis, but this idea has been pretty much abandoned and it is felt that it is more of a manifestation of liver damage. Leukopenia and eosinophilia were thought to be of some significance, but analysis of large series of cases fails to bear this out. Kunkel and Yesner²⁸ review seven cases of thrombocytopenic purpura associated with sarcoidosis of the spleen found in the literature and add one of their own which was relieved by splenectomy.

Hepatic Involvement: Impairment of liver function in sarcoidosis is believed to be the basis for the alteration in the serum proteins so frequently found in this disease. Harrell,²⁷ studying the fractional precipitation curves of blood serum, compared the curves of sarcoidosis patients with those of patients who had all types of liver disease other than sarcoidosis, and found a great similarity between the two. He also observed substances resembling Bence Jones protein in the urine of these sarcoidosis patients, and expressed the belief that these findings indicate abnormal hepatic protein metabolism in this disease. In these same patients he found diminished bilirubin tolerance when tested and compared with normal individuals. It is his belief, furthermore, that even in the absence of clinical liver involvement there actually exists a more serious functional and histopathologic hepatic damage than is commonly recognized. The observations of many investigators since that time have strongly confirmed this belief, and by extensive biopsy and autopsy studies have shown that, next to the lymph nodes and lungs, the liver shows the greatest frequency of involvement.

In the past, hepatomegaly has been used as a criterion for involvement of that organ by the sarcoid process; but in a disease which produces such a high incidence of severe pulmonary damage, with its ensuing pulmonary fibrosis, right heart strain and failure resulting in hepatic engorgement from the passive congestion, the use of hepatomegaly as a criterion seems no longer tenable.

Table 4 briefly presents some of the interesting findings concerning the liver which 21 groups of investigators have brought forth during the past 15 years either through study of the liver directly or through interest in sarcoidosis as a disease entity which involves many organs and tissues throughout the body.

COMMENT

Because of the lack of uniform standards for the definition of hyperglobulinemia and hyperproteinemia, no actual statistics can be compiled in regard to this phase of the abnormal metabolism; but it is the impression of the authors that a conservative 62 per cent of all sarcoidosis patients will show a serum globulin level over 2.75 gm./100 c.c. during some phase of their disease, and that the finding of a total serum protein over 7.75 gm./100 c.c. is much less common than has been assumed in the past.

Of the eight liver biopsies done on the 12 patients who showed frank jaundice, two revealed the histopathologic picture of an alcoholic cirrhosis (Laennec type) which coincided with a history of chronic alcoholism in both instances, two more cases were complicated by hemolytic anemia, and the fifth had positive tuberculin tests and, although the initial biopsy was quite suggestive of sarcoidosis, the lesions could not be demonstrated later by liver sections taken at the time of laparotomy.

Of note also is the infrequent appearance of jaundice or serum bilirubin levels of any magnitude, and the high correlative incidence of liver biopsies showing the presence of the typical sarcoid tubercles in groups of patients who had previously had a presumptive or clinical diagnosis of sarcoidosis already established. This latter observation will be highlighted in our study of 1,126 liver biopsies as reported in the literature.

In 1938 Snapper and Pompen³⁰ became interested in the visceral localization of the granulomatous sarcoid lesions, but it was not until 1942 at the Massachusetts General Hospital³¹ that the first sarcoid nodules were found by liver biopsy during the course of peritoneoscopy.

From that time until five years ago comparatively little attention was paid to the liver in the study of sarcoidosis, but since 1948 a great many investigators have focused their efforts on this aspect of the disease, and our knowledge of the pathology and pathologic physiology of this organ is gradually expanding.

COMMENT

The results of the tables are self-explanatory and show the general incidence of sarcoidosis as a cause for liver disease (2.0 per cent), and the high

TABLE IV
Liver Involvement as Shown by Clinical Studies on Sarcoidosis Patients

Investigators	No. of Cases Reported	No. of Cases of Hepatomegaly	No. Cases Described as Showing Clinical Liver Involvement	No. Cases Showing Frank Jaundice and Bilirubin Over 1.0 mg. %	No. of Cases with Liver Biopsy	No. of Biopsies Pos. for Sarcoid	Results of Liver Function Tests and Comments
Harrell ²⁷	11	6	4	—	—	—	A/G ratio reversed in all "active" cases.
Katz, Cake and Reed ²⁸	10	1	1	—	—	—	Majority of cases showed hyperglobulinemia.
Riley ²⁹	52	19	0	0	—	—	68% had elevated serum globulin. 47% had elevated serum alkaline phosphatase. 45% had positive cephalin cholesterol flocculation.
Ricker and Clark ³⁰	300	17 of 195	—	—	—	—	In 33% of 40 cases the protein exceeded 8.0 gm. In 60% of 31 cases the globulin fraction exceeded 3.0 gm.
Oblath and Farber ³¹	40	16	—	—	1	1	53% of 32 cases had elevated globulin.
Vivas, Smith and Jacobs ³²	20	5	—	—	—	—	The average serum protein in this series was 6.9 gm. with albumin 3.75 gm. and globulin 3.18 gm.
Harrell and Fisher ³³	11	—	3	—	—	—	Blood alkaline phosphatase was elevated in "active" cases. Majority had hyperglobulinemia.
Hunnicutt, Nushan and Miller ³⁴	38	—	1	—	—	—	58% of this series had reversal of A/G ratio.

TABLE IV—Continued

Investigators	No. of Cases Reported	No. of Cases of Hepatomegaly	No. Cases Described as Showing Clinical Liver Involvement	No. Cases Showing Frank Jaundice or Total Serum Bilirubin Over 1.0 mg. %	No. of Cases with Liver Biopsy	No. of Biopsies Positive for Sarcoid	Results of Liver Function Tests and Comments
Curtis and Grekin ²⁴	—	—	—	—	—	—	Authors summarize their experience with sarcoidosis and the literature and conclude, "Jaundice is an unusual occurrence." When liver is enlarged the edge is usually firm, smooth and only slightly tender.
Klatskin and Yesner ²⁵	15	11	12	5 (2 had serum bilirub. >1.2 mg. %)	15	15	53% showed hyperglobulinemia, 53% a prothrombin time less than 70% of normal, 53% thymol turbidity over 5.0, 40% alk. phosphatase over 5 Bodansky units and 35% a BSP retention over 6% (45 min.).
Longcope and Freiman ²⁶	142	35	—	1	7	5	In 18 of 33 or 54.5% protein was over 7.5 gm. but not over 10.0. In 19 of 28 the globulin was over 3.0 gm. or 68%.
Mino, Murphy and Livingstone ²⁷	1	1	1	—	1	1	Report of a severe case of portal hypertension caused by intrahepatic sarcoid with relief of pressure by splenorenal shunt but little change in serum proteins, or ceph. flocc. or prothrombin time postoperatively.
Cameron and Dawson ²⁸	1	1	—	—	1	1	Typical case sarcoidosis with splenectomy done for unspecified reason. Hepatomegaly with rt. heart failure but characteristic lesions present. Hepatocellular degeneration thought part of heart failure.

TABLE IV—Continued

Investigators	No. of Cases Reported	No. of Cases of Hepatomegaly	No. Cases Described as Showing Clinical Liver Involvement	No. Cases Showing Frank Jaundice or Icteric Secretion Bilirubin Over 1.0 mg. %	No. of Cases with Liver Biopsy	No. of Biopsies Pos. for Sarcoid	Results of Liver Function Tests and Comments
Crane and Zetlin ⁴³	1	1	0	1	1	0	Lymph nodes showed typical lesions but patient with jaundice died in hemolytic crisis. Liver not involved at autopsy.
Goeckermann ⁴⁴	17	—	—	2	—	—	Comments on rarity of jaundice in sarcoidosis, but when present may be caused by extrinsic pressure of enlarged lymph nodes on biliary tracts.
Longcope and Pierson ⁴⁵	8	2	—	2	—	—	Comment on infrequent appearance of jaundice in sarcoidosis.
Dickie and Middleton ⁴⁶	11	1	1	1	1	?	Liver biopsy in only case of jaundice in this series of histologically proved sarcoidosis was positive but later, at laparotomy, no sarcoid lesions could be found. On section—only cirrhosis and hepatocellular degeneration. A/G ratio 1:1. Ict. ind.—20.
Ross and Weinberg ⁴⁶	2	—	2	2	2	2	Reported as case of sarcoidosis causing regurgitation jaundice. Serum protein normal early but later A/G ratio reversed, ceph. flocc. and thymol turb. strongly positive and alk. phos. elevated. Serum bilirubin averaged 2.1 to 3.1 mg. %.
Nadler ⁴⁷	5	0	2	1	1	?	Five cases of splenectomy for hypersplenism with one liver biopsy showing tubercles with central necrosis but no organisms seen or cultured. Cause of icterus unknown.

TABLE IV—Continued

Investigators	No. of Cases Reported	No. of Cases of Hepatosplenomegaly	No. Cases Described as Showing Clinical Liver Involvement	No. Cases Showing Frank Jaundice or Total Serum Bilirubin Over 1.0 mg. %	No. of Cases with Liver Biopsy	No. of Biopsies Pos. for Sarcoid	Results of Liver Function Tests and Comments
Shay, Berk et al. ⁴⁸	24	7	21	6	21	16	While 6 cases had serum bilirubin over 1.0 mg. %, none was over 1.5 mg. %. Positive Kunkel test (gamma glob. flocc.) in 21 cases. BSP retention over 4% (30 min.) in 14 cases. Relative hyperglobulinemia. Tissue alk. phosphatase increased around areas of the granulomata.
Dagradi, Solled and Friedlander ⁴⁹	1	1	1	1	1	1	Case of sarcoidosis with jaundice and hepatosplenomegaly. Alk. phos., serum bilirubin, cholesterol, serum globulin and urinary urobilinogen all elevated. Ceph. chol. flocc. and thymol turb. both strongly pos.

SUMMARY OF TABLE IV

Total number of cases of sarcoidosis reported.....	710
Number of cases with hepatomegaly.....	124
Number of cases with clinical evidence for liver involvement.....	50
Number of cases with frank jaundice or serum bilirubin over 1.0 mg. %.....	22
Number of cases in which liver biopsy was done.....	52
Number of biopsies showing conclusive evidence for sarcoidosis.....	42
Number of biopsies showing questionable evidence for sarcoidosis.....	2
Number of cases of frank jaundice irrespective of serum bilirubin level.....	13
Number of liver biopsies in this group alone.....	8
Number of biopsies positive for sarcoidosis in this group.....	3

TABLE V

Liver Involvement as Shown by Biopsy Studies on Patients with Presumptive Diagnosis of Sarcoidosis Made Prior to Biopsy

Investigators	Number of Cases Biopsied	Number of Positive Biopsies
VanBeek and Haex ⁴⁰	4	2
VanBuechem ⁴¹	14	11
Klatskin and Yesner ²³	20	15
Baird, Bogach and Fenwick ⁴²	3	3
Dagradi, Sollod and Friedlander ⁴³	1	1
Shay, Berk et al. ⁴⁴	21	16
Totals	63	48
Percentage of positive results in this series 76.25%		

correlative incidence of positive liver biopsies in groups of patients who had previously had a presumptive or clinical diagnosis of sarcoidosis already established.

One might infer from these data that, were one to do liver biopsies as a routine screening measure on large segments of the population at large, one would miss the diagnosis of sarcoidosis in only 25 per cent of all cases so tested. This is purely a speculative comment and is not recommended for actual practice because of the hazards connected with the procedure and because it is impractical to use such methods in screening for a disease of such comparative benignity and infrequency.

Much information regarding the behavior of sarcoidosis has been gained from autopsy cases. Pinner ¹¹ and Rubin and Pinner ¹⁵ did the initial work in attempting to summarize and correlate all the autopsy findings in cases of sarcoidosis up to 1944. Because of their belief that sarcoidosis was one aspect of tuberculosis, their summaries (and their own two cases) included not only cases of clear-cut sarcoidosis but also cases with concomitant tuberculosis and, in a few instances, cases of primary, full-blown active tuberculosis. However, other investigators have done the same thing, and it is difficult to establish a definite line of demarcation in separating the reports on these two diseases.

Since that time Friedman, ⁷⁸ Granström, Gripwall et al., ⁸² Ricker and Clark, ¹⁹ Klatskin and Yesner ²³ and Ustvedt ¹⁸ have not only summarized the 44 cases of Rubin and Pinner ¹⁵ but also have added autopsy reports of

TABLE VI

Liver Involvement as Shown by Routine Biopsy Studies on All Patients with Liver Disease from All Causes

Investigators	Number of Cases Biopsied	Number of Positive Biopsies
Volwiler and Jones ⁵⁴	171	2
Scadding ⁵⁵	80	3
Klatskin and Yesner ²³	650	15
Cassel ⁵⁶	162	2
Totals	1,063	22
Percentage of positive results in this series 2.0%		

their own until, in 1949, the total had been brought up to approximately 90. Because of the danger of overlapping and reduplication in these summaries, the original literature was consulted with the exception of six cases in Pinner's series, where the journals containing the original articles were not available, and six other cases reported in the literature with unspecified or obscure references. Forty-eight more autopsy reports in cases of sarcoidosis were thus discovered, so that, with the report included in this article, the total is brought up to 139. Recently Longcope and Freiman,²⁵ in a monograph outstanding for its comprehensiveness and analysis of statistics, reported 30 autopsies from their examination of the records of their own patients and those of the Johns Hopkins Hospital and the Massachusetts General Hospital. However, these data were not included in this report, as so many of the autopsy protocols had already been published; they are included under the original authors' names in table 7.

DISCUSSION

In analyzing statistics from the literature on sarcoidosis, it is extremely difficult to get a clear, concise picture of the disease as an entity because of the different facets of the disease emphasized by each investigator and colored by his own personal interest in the disease. As Klatskin and Yesner²³ point out in their excellent study of sarcoidosis and other granulomatous diseases, the differentiation of sarcoidosis from tuberculosis, leprosy, brucellosis, beryllium poisoning, erythema nodosum, infectious mononucleosis, blastomycosis, coccidioidomycosis, and even syphilis may at times be quite difficult. There are now well over 2,000 reported cases of sarcoidosis. The diagnosis of most of these cases is fairly well substantiated by microscopic tissue examination, but in many cases diseases causing similar lesions have not been excluded, or the cases presented are complicated by concomitant disease processes which may masquerade as sarcoidosis.

The diagnosis rests on a number of factors. A presumptive diagnosis should be made on at least two or more of the following findings: chest x-ray films showing parenchymal involvement either with or without mediastinal or tracheobronchial lymph node enlargement, enlarged peripheral nodes, enlarged liver or spleen, cystic changes in the small bones of the hands or feet on x-ray examination, the presence of flat-topped, violaceous papules in the skin, inflammation of the eyes (which according to Heerfordt¹²⁷ may be ushered in by fever and swelling of one or more of the salivary glands—so called uveoparotid fever), and alteration in the serum proteins with a relative hyperglobulinemia. More recently, attention has been called to hypercalcemia, thrombocytopenia, leukopenia and eosinophilia as possible additional diagnostic findings. More work along these avenues of investigation must be done before any definite correlative value can be attached to such findings.

Intracutaneous tuberculin tests are negative in about 90 per cent of the

TABLE VII
Liver Involvement in Sarcoidosis as Shown by an Analysis of 138 Autopsies

Investigators	No. of Autopsies	Gross Liver Involvement	Microscopic Liver Involvement and Comments
Adickes et al. ^{57*}	1	None	Yes—diffuse parenchymal lesions. F—cardiac
Bates and Walsh ^{58*}	1	Yes	Yes—diffuse parenchymal lesions. F—cardiac
Beintema ⁵⁹	1	None	None. F—CNS
Berblinger ⁶⁰	1	Yes	Yes—lesions described as corresponding to Schuppel's lymphoma of Von Recklinghausen or the large cell tuberculous hyperplasia of Ziegler. Also ?purpura. Tbc.
Berg and Bergstrand ⁶¹	1	Not mentioned	Not mentioned. F—cor pulmonale
Berg ⁶²	1	None	None. F—?CNS
Bergmann ⁶³	1	Yes	Yes—lesions in liver capsule. Tbc.
Bernstein et al. ^{64*}	1	Yes	Yes—one lesion found and sectioned. F—hydrothorax
Bernstein and Oppenheimer ⁶⁵	1	Questionable	None—only chr. passive cong. F—cor pulmonale
Blum and Mitchell ⁶⁶	1	None	Yes—lesions in portal triad. F—G.I. Hemorrhage and purpura
Botman ⁶⁷	2	Yes	Yes—(2) Other data not available.
Bour ⁶⁸	1	Yes	Yes—(1) Other data not available.
Capuani ⁶⁹	1	Yes	Yes—few isolated granulomata scattered throughout the liver. F—cor pulmonale
Case # 38082 ⁷⁰	1	Yes	Yes—lesions in periportal area. F—cor pulmonale
Clearkin et al. ⁷¹	1	None	None. F—?cor pulmonale
Cotter ^{72*}	1	Yes	Yes—numerous miliary tubercles with periportal arrangement. F—cor pulmonale
Courmont et al. ⁷³	1	Not mentioned	Not mentioned. F—pulm. hemorrhage
Crane and Zetlin ⁷⁴	1	None	None. F—purpura
Danbolt and Hval ⁷⁵	1	None	None. F—carcinoma
Deelman ⁷⁶	2	Yes	Yes—(2) Other data not available.
Enzer ⁷⁶	1	Not mentioned	Not mentioned. F—purpura
Erickson et al. ⁷⁷	1	Liver not examined due to limited autopsy permission.	F—CNS ID
Friedman ⁷⁸	1	Yes	Yes—one lesion found. F—men. meningitis and RVHD
Froehlich and Scherer ⁷⁹	1	Yes	Yes—diffuse lesions throughout. F—cor pulmonale
Garland and Thompson ^{80*}	1	None	Yes—thought to have Tbc. but none found.
Gendel et al. ⁸¹	3	Yes (3)	Yes—(2). F—2 cor pulm. and 1 spont. pneumothorax.
Granström et al. ⁸²	1	Yes	Yes—sparsely disseminated submiliary tubercles in periportal tissue.
Hirsch ⁸³	8	Not mentioned	Yes—(2) Sarcoidosis not mentioned in this paper but criteria for diagnosis present.
Hogan ⁸⁴	1	Not mentioned	Not mentioned. ID
Hollister and Harrell ⁸⁵	1	Yes	Yes—caseating tubercles in parenchyma. Tbc.
Johnson and Jason ^{86*}	1	Not mentioned	Yes—diffuse distribution. F—cor pulm. ?cardiac
Jonas ^{87*}	5		Yes—(5); syphilis—(1). F—4 cardiac. 1 tox. thyroid

* Indicates cases reported with specific cardiac involvement.

Tbc., Asb. or ID: Indicate cases with proved tuberculosis or asbestosis or insufficient data and are not counted in the final tabulation.

F—Indicates either cause of death, if reported, or probable cause of death surmised from the data presented.

TABLE VII—Continued

Investigators	No. of Autopsies	Gross Liver Involvement	Microscopic Liver Involvement and Comments
Katz, Cake and Reed ⁸⁸	1	Yes	? Yes—liver studded with small sarcoid nodules. F—cor pulmonale
King ⁸⁹	1		? Yes—liver described as being involved. F—? cor pulmonale
Klatskin and Yesner ⁹⁰	1	Questionable	Atypical granulomata observed with Laennec's cirrhosis also present.
Kraus ⁹¹	1	Questionable	Atypical granulomata observed. F—pituitary dyscrasia and purpura
Kulka ⁹²	1	None	Yes—liver studded with tubercles. F—cardiac
Lenartowicz and Rothfeld ⁹³	1	None	Yes—tubercles in periportal areas. F—CNS
Longcope ¹⁷⁹	4	Yes (3)	Yes—(3) typical liver nodules. Tbc. (1 only)
Lopes de Faria ⁹⁴	1		— ID
McCort, Wood et al. ¹⁸	1	Yes	? Yes—typical granulomatous lesions seen. F—cor pulmonale
Michalik ⁹⁵	1	None	None—Tbc.
Mylus and Schürmann ⁹⁶	1	Yes	Yes—caseating granulomata of liver seen but no acid-fast organisms found. F—cor pulmonale
Naumann ⁹⁵	1	Yes	Yes—typical lesions in 3 mos. child.
Nestmann ⁹⁶	2	Yes (2)	Yes—(1) Tbc. (1 only)
Nickerson ²⁷⁹	6	Yes (4)	Yes (4)—Greatest involvement in portal fibrous tissue, lesser in mid-zonal lobular areas. F—1 cardiac, 3 pneumonia, 2 intracran. hem.
Nicod ⁹⁸	1	Not mentioned	Not mentioned. F—? CNS
Nieuwenhuijse ⁹⁹	1	Yes	Yes—one nodule found. F—pancreatitis and peritonitis
Pinner ¹⁰⁰	1	None	None. Tbc.
Posner ¹⁰¹	1	Questionable	Questionable. Collections of epithelioid cells were seen with no necrosis or giant cells in a cirrhotic liver.
Pruvost et al. ¹⁰⁰	1	Yes	Yes—tubercles with necrotic centers seen in periportal spaces. Tbc.
Reisner ¹⁰	2	Not mentioned	Not mentioned. 2—Tbc.
Ribaud ^{102*}	1	None	None. F—CNS hemorrhage.
Ricker and Clark ¹⁰³	22		Liver described as being involved in 18 cases with typical lesions in characteristic location. Three deaths definitely due to sarcoidosis. Possibly two others. 1—cor pulmonale, 1—cardiac, 1—CNS, ? 1—cerebral hem., ? 1—pulm. hem.
Riley ⁹²	5	Yes (3)	Yes—(3) lesions scattered throughout parenchyma and periportal spaces. 4F—cor pulmonale
Ronchese ¹⁰⁴	1	Not mentioned	Not mentioned. Tbc.
Rosenthal and Feigen ¹⁰⁵	4	Yes (1)	Yes—(1) "clumps of eosinophilic material seen within portal canals"—also hyalinized lesions of portal area. 1F—cerebral throm., 1F—S.B.E., 1F—Pn. and Pn. meningitis. (1) Tbc.
Rubin and Pinner ¹⁵	1	Six liver abscesses found to contain acid-fast organisms.	Tbc.
Schaumann ^{106*}	1	Yes	Yes. F—emphysema and cor pulmonale
Schaumann ¹⁰⁷	2	Yes (1)	Yes—(1) This case died of influenza. (1) Tbc.
Scheidegger ¹⁰⁸	1	Not mentioned	Not mentioned. F—CNS
Schlagenhaufen ¹⁰⁹	1	None	None. F—cause ?

TABLE VII—Continued

Investigators	No. of Autopsies	Gross Liver Involvement	Microscopic Liver Involvement and Comments
Scotti and McKeown ^{110*}	1	None	Yes—typical nodules usually found in the periphery of lobules and occasionally in mid-zonal areas. F—cor pulmonale
Skavlein and Ritterhof ¹¹¹	1	Yes	Yes—typical nodules found but were asbestosis.
Smith and Sauls ¹¹²	1	None	None—Only chr. passive cong. F—ASHD and diabetes
Spencer and Warren ^{113*}	1	Yes	Yes—typical granulomata scattered indiscriminately without regard for zone. F—edema of larynx (sarcoid involvement)
Stein ^{114*} ?	1	None	None—Had fibrosis left ventricle. F—CNS
Strümpke ¹¹⁵	1	None	None—Tbc.
Teilum ¹¹⁶	1	None	Yes—typical lesions found but pt. had Tbc.
Thomas ³¹	1	Not mentioned	Not mentioned. F—amyloidosis
Tice and Sweany ¹¹⁷	1	None	None. F—cor pulmonale
Tillgren ^{118*} ?	1	—	Yes—typical microscopic lesions seen. F—pituitary
Uehlinger ¹¹⁹	1	Not mentioned	Not mentioned. F—CNS
Ustvedt ^{120*}	1	Yes	Yes. F—cor pulmonale
Voldet ¹²⁰	2	None (2)	None—(2) (2) F—cor pulmonale
Wahlgren ¹²¹	1	Not mentioned	Not mentioned. F—cor pulmonale
Walz ¹²²	1	Not mentioned	Not mentioned. F—Tbc.
Warren and Sommers ¹²³	3		Yes—(2) Question of relationship between cicatrizing enteritis and sarcoidosis.
Yesner and Silver ^{124*}	1		Yes—lesions mostly in portal triads. F—cardiac
Zimmerman and Mann ¹²⁵	1	Yes	Yes—widely diffused discrete nodules. F—cor pulmonale
Zollinger and von Meyenburg ¹²⁶	1	None	None. F—CNS

SUMMARY OF TABLE VII

	No.	Per Cent
I. TOTAL NUMBER AUTOPSIES (reported as sarcoidosis).....	138	
Cases tuberculosis (primary or associated with sarcoidosis).....	17 or 12.3%	
Cases asbestosis.....	1	
Cases with data too inadequate to be included in tabulation.....	3	
II. REMAINING CASES OF SARCOIDOSIS (primary diagnosis).....	117 or 84.7% of I	
Number cases in this group with conclusive histopathologic sarcoid liver involvement.....	78 or 66.5% of II	
Number of cases in which liver is not mentioned.....	8 or 6.8% of II	
Number of cases showing no liver involvement.....	31 or 26.5% of II	
III. TOTAL NUMBER DEATHS ATTRIBUTABLE TO SARCOID INVOLVEMENT OF SPECIFIC ORGANS.....	55 or 47.0% of II	
(a) Pulmonary involvement with right heart failure (cor pulm.)...	27 or 49.0% of III	
(b) Central nervous system involvement.....	10 or 18.2% of III	
(c) Myocardial and/or epicardial involvement.....	10 or 18.2% of III	
Pulmonary hemorrhage.....	1 or 1.8% of III	
Repeated and massive gastrointestinal hemorrhages.....	1 or 1.8% of III	
Spontaneous pneumothorax (rupture emphysematous bleb).....	1 or 1.8% of III	
Massive hydrothorax.....	1 or 1.8% of III	
Laryngeal edema (extensive involvement of vocal cords).....	1 or 1.8% of III	
Pituitary gland involvement.....	1 or 1.8% of III	
Compression of great vessels.....	1 or 1.8% of III	
Uremia caused by extensive renal involvement.....	1 or 1.8% of III	
HEPATIC INVOLVEMENT.....	NONE	

SUMMARY OF TABLE VII—Continued

- IV. Total number deaths attributed to sarcoidosis but actual mode of death and specific tissue involvement which might have proved fatal not definite..... 15 or 12.8% of 11
- V. Total number of deaths due to specific causes other than sarcoidosis 47 or 40.2% of 11
- (Note—(a), (b) and (c) each contain three questionable cases and might well contain two or three cases more each in which the cause of death was due in all probability to the organs specified.)

ADDITIONAL DATA GATHERED FROM REVIEW OF THE AUTOPSIED CASES

Average age at time of death.....	34.2 years
Percentage of males in this autopsy series.....	60.0%
Percentage of organ involvement found in the 117 cases (II.)	

Lymph nodes.....	77.7%	Thyroid.....	4.2%
Lungs.....	77.0%	Intestine.....	3.4%
Liver.....	66.5%	Stomach.....	2.5%
Spleen.....	49.5%	Pituitary.....	2.5%
Heart.....	19.6%	Adrenals.....	0.85%
Skin.....	16.2%	Pancreas.....	0.85%
Bones.....	16.2%	Prostate.....	0.85%
C.N.S.....	7.7%	Testes.....	0.85%
Kidney.....	6.8%	Ureters.....	0.85%
Oculoparotid.....	6.0%	Epididymis.....	0.85%

cases. The Kveim reaction may be of diagnostic value, but it is not specific, takes at least three to six months to read, is a very painful one for the patient and, according to Faulk and Moschella,¹²⁸ may cause a serious degree of necrosis at the site of injection which may take many weeks to heal. Many authorities feel that the Kveim reaction is likely to be positive only in those cases which show activity or progression of signs and symptoms. Putkonen¹²⁹ found that 33 of 42 proved cases of sarcoidosis had positive reactions while skin lesions were present, but that all those with healed skin lesions gave a negative response. However, the skin reactions differed from those of 50 controls only in the degree of severity, and Nelson¹³⁰ found the test negative in several cases which he considered to be actively progressive. In several patients he injected normal spleen prepared in the same way as the Kveim antigen, and obtained results identical with those when using antigen prepared from known sarcoid skin, lymph node and splenic tissue.

The positive diagnosis of the disease must rest on the finding of the typical granulomatous lesions on microscopic examination of the various tissues biopsied or sectioned, thus helping to exclude Hodgkin's disease, lymphosarcoma, carcinoma, Banti's syndrome and leukemia. Guinea pig inoculations of body fluids, secretions, excretions and gastric washings, along with careful skin testing, serologic studies, agglutination reactions, bacteriologic smears and cultures and hemocytologic studies, will be of help in ruling out tuberculosis, leprosy, brucellosis, leukemia, infectious mononucleosis, coccidioidomycosis, blastomycosis and syphilis. The occupational history is of value in ruling out asbestosis, silicosis and beryllium poisoning.

The liver affords an interesting field for investigation in this disease, and the alteration in the serum proteins and other aspects of liver function,

along with the mechanism responsible for the rare case of jaundice, are processes the pathogenesis of which is still open to speculation. In a final correlative analysis of the data presented in tables 3, 4, 5, 6 and 7 (eliminating duplication of cases and eliminating reports of hepatomegaly and biopsies as criteria for purely clinical involvement in this particular instance), we find that 80 out of 581 clinically studied cases (or 13.75 per cent) show abnormalities in one or more liver function tests exclusive of serum protein determinations. Our criteria for abnormal reaction in these tests is as follows: thymol turbidity, over 5; cephalin cholesterol flocculation, 2 plus or over; total serum bilirubin, over 1.0 mg. per cent; bromsulfalein retention, over 6 per cent in 45 minutes; prothrombin time, less than 70 per cent of normal; and alkaline phosphatase, over 5 Bodansky units.

However, if we include hyperglobulinemia (average globulin level, over 2.75 gm./100 c.c.) in the criteria for abnormal hepatic function and evidence for clinical involvement, our total increases from 80 to 193 cases out of 318 in which serum protein studies were conducted, or a percentage of 60.75. If, however, we use the total number of cases (709) reported by these same investigators, instead of just the number of those with appropriate laboratory studies, the incidence drops to 27.2 per cent. In other words, only 318 cases out of a grand total of 760 cases studied clinically by all investigators have had adequate laboratory investigations. This discrepancy is gradually being reduced as the awareness of the rôle of the liver in this disease becomes more acute.

As noted before, hepatomegaly per se should not be used as a criterion for sarcoid involvement of that organ, but for the sake of completeness of the statistical analysis it is of interest to note that the liver was found to be enlarged in 135 cases out of 581 in which note was made of abdominal palpation, or out of a total of 686 cases reported by these same authors. This is an incidence of 23.2 per cent and 19.65 per cent respectively.

It seems reasonable to suppose that the cause for the faulty hepatic metabolism is primarily the pressure on, and replacement of, normal healthy liver cells by the granulomatous nodules themselves, and the concomitant and ensuing fibrosis and hyalinization, rather than an inherent hepatocellular degeneration per se. It also seems likely that pressure on the portal triads from the same cause might well produce jaundice when abnormal icterus does occur. Crane and Zetlin⁴³ and Goeckermann⁴⁴ bring up the question of extrinsic pressure of enlarged lymph nodes on the larger extrahepatic biliary tracts. Jaundice itself is rare indeed in this disease, and in only three previous cases out of 867 clinical and autopsied cases reported so far was the jaundice definitely proved to have been caused by sarcoid involvement of the liver. This is particularly surprising in view of the fact that 76 per cent of livers will show involvement by biopsy, and 66.5 per cent of livers in such patients have been shown to be involved by autopsy examination.

The disease tends to run a chronic course. The greater the number of

tissues or organs involved, and the greater the involvement within each organ, the less likely is there to be a complete and spontaneous remission. Mortality statistics vary from as high as 28 per cent to as low as 1.5 per cent. It is our feeling that an estimated 3 per cent is a fair and conservative representation of the death rate in this disease.

There has been no specific treatment for sarcoidosis up to the present. ACTH and cortisone are currently receiving much attention, and a number of investigators have reported encouraging results after using these steroids in an effort to arrest the progress of the disease. However, the time interval for observation and follow-up is of insufficient duration and the cases treated thus far are too few for any definite conclusions to be drawn from this form of therapy at the time of this writing.

SUMMARY

A case of sarcoidosis is presented in which the clinical features were those of severe liver disease, namely, jaundice, ascites, serum protein alteration and inanition leading to death. In this case the diagnosis was established on the histopathology of the skin lesions three years prior to death, and the absence of evidence for other granulomatous diseases occurring either primarily or concomitantly with the sarcoidosis. Autopsy examination confirmed the diagnosis and revealed the extensive liver involvement. The cirrhotic changes, we believe, were definitely produced by the sarcoid disease. The destruction of the hepatic architecture and the extensive fibrosis thus produced were the cause of the bile stasis and jaundice, ascites and disturbance in hepatic metabolism.

Six hundred fifty-six cases of sarcoidosis were reviewed from a clinical standpoint, 710 cases were examined from reports in the literature for clinical features of liver involvement, 1,106 liver biopsy reports were studied for evidence of histopathologic liver involvement, and 138 autopsy reports were likewise culled in an effort to understand the type, mode and frequency of involvement of the liver in sarcoidosis.

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CASE REPORTS

JAUNDICE DUE TO METHYL TESTOSTERONE THERAPY *

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THERE is increasing evidence that a distinct type of hepatic damage is produced in some patients by administration of methyl testosterone. We have found reports of 18 such cases in the medical literature.^{1, 2, 4, 5, 7} References by many authors to unpublished observations of a similar nature suggest that the actual number of cases is much greater. As we become more aware of jaundice as a possible effect of methyl testosterone, we may expect this condition to be recognized more frequently.

The patient whose record is summarized here developed severe jaundice of the type first reported by Werner in 1947.¹ A prolonged observation led us to conclude that the condition could not be attributed to any of the more usual forms of biliary obstruction or hepatic damage. We believe that the findings are satisfactorily explained as a complication of therapy with methyl testosterone in which severe and sustained jaundice is not accompanied by evidence of hepatocellular damage. As in previously reported instances, apparent complete recovery followed cessation of the medication.

CASE REPORT

The patient, a white female 45 years of age, was admitted to the University Hospital on November 18, 1952, with a chief complaint of increasing jaundice of two weeks' duration and semicoma of four hours.

Two weeks prior to the present admission the patient and her children had noticed that her skin was turning yellow. The patient also noticed that her urine had become dark in color and that her stools were a light yellow. Since the onset of the jaundice the patient had become intolerant of greasy or fatty foods, which she vomited a few minutes after ingestion. She denied any abdominal pain during or prior to the advent of the jaundice, but she had experienced a sensation of tightness or fullness in the epigastrium. For the two days immediately preceding admission to the hospital she had suffered from shooting pains in the anterior portion of the left chest in the area below the fifth rib. The episode of semicoma was the third such attack that she had experienced, and was abolished by administration of intravenous glucose.

The patient had had the usual childhood diseases. Her mother had told her that she had had an attack of jaundice as a child, but she knew nothing of the details of this episode. She had been admitted to the University Hospital on four previous occasions and had been seen in the Emergency Room on three previous occasions. She was admitted to the hospital in 1944 for a normal delivery. In April, 1945, she was readmitted for management of an adherent placenta that was a complication of a home delivery. The placenta was removed manually. Secondary anemia due

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to extensive blood loss and puerperal sepsis further complicated this delivery. On September 13, 1945, the patient was treated in the hospital for chronic cervicitis, second degree laceration of the perineum and mild chronic endometritis.

In April, 1952, the patient was admitted to the hospital with complaints of loss of libido, loss of pubic and axillary hair, amenorrhea and atrophy of the breasts. A diagnosis of postpartum pituitary necrosis was made.

Laboratory studies performed on April 21, 1952, revealed a fasting blood sugar of 42 mg. per cent; a nonprotein nitrogen of 59.5 mg. per cent, and plasma proteins of 6.0 gm. per cent. The albumin-globulin ratio was 1.4/1. A glucose tolerance test was performed on the following day. The fasting blood sugar was 107 mg. per cent; the values at 30 minutes and at one, two and three hours were 292 mg., 207 mg., 126 mg. and 93 mg. per cent, respectively. The serum calcium was 10.8 mg. per cent; the inorganic phosphorus was 4.7 mg. per cent; the serum sodium was 129.3 mEq. per liter, or 296.5 mg. per cent; the serum potassium was 4.54 mEq. per liter, or 18.15 mg. per cent. The serum cholesterol was 225 mg. per 100 ml. The thymol turbidity was 13.5 units, and the cephalin-cholesterol flocculation test was negative in 24 and 48 hours. The serum bilirubin was 0.95 mg. per cent, and the alkaline phosphatase was 4.35 King-Armstrong units. An intracutaneous tuberculin test, using 0.1 ml. of a 1-1000 dilution of OT, was negative at 24 and 72 hours. Determinations of the basal metabolic rate were reported as minus 3 and minus 5.

Two weeks later an eosinophil fluctuation test was performed. The original count was 314 eosinophils per cubic millimeter. Four hours after the administration of 4 mg. of adrenalin the count was 198 cells per cubic millimeter. The 24 hour excretion of 17-ketosteroids determined on the same day was 3.6 mg.

The regimen of therapy outlined for the patient was not ideal but was considered to be adequate and within her financial means. She was advised to take 4 gm. of sodium chloride daily; 16 mg. of desiccated thyroid daily for four weeks, then 32 mg. daily; 10 mg. of methyl testosterone daily; and 10 mg. of diethylstilbestrol daily for four weeks, then 20 mg. daily. A diet high in carbohydrate and protein was advised. Approximately four months later the methyl testosterone was increased to 20 mg. daily. The patient experienced episodes of hypoglycemia and coma on June 12, November 1 and November 18, 1952.

The physical examination at time of this admission (November 18, 1952) revealed: temperature, 98.0° F.; pulse, 64 per minute; respirations, 16; blood pressure 90/60 mm. of Hg. The patient was a well developed, poorly nourished white female, appearing very jaundiced and chronically ill but not in acute distress. The skin was smooth and warm to touch. No petechiae or spider hemangiomas were noted. The breasts were atrophic. Fine crepitant râles were noted in the bases of both lungs, more pronounced on the right side. No friction rubs or dullness to percussion were noted. No abnormality of the heart was detected. The liver was palpable 3.5 cm. below the right costal margin, and was soft and nontender. Diastasis recti was present, and many striae of pregnancy were noted. The vulvae were bluish and atrophic and there was an absence of pubic hair. The vagina showed some thinning of the mucosa. No cervix was noted, but a small fibrous band occupied the normal site of the cervix. No tenderness or masses were felt in the region of the adnexae. Rectal examination revealed no abnormality. The extremities were normal, and no pathologic reflexes were elicited. The provisional diagnosis was (1) postpartum pituitary necrosis (Sheehan's disease); (2) jaundice of undetermined etiology.

Course in the Hospital: The therapeutic regimen instituted in the out-patient department was continued except that after two days the diethylstilbestrol was reduced from 10 mg. twice a day to 5 mg. twice a day. The patient continued to complain of chest pain until the night of November 22. On November 24 a needle biopsy of the liver was performed, employing the transthoracic approach. The microscopic

appearance of the tissue suggested plugging of the canaliculi by bile, with no appreciable hepatocellular damage. Figure 1 is a photomicrograph of a hematoxylin-eosin preparation of the tissue obtained by the needle biopsy. The patient was discussed at a joint conference of the Medicine and Surgery Departments on December 2. At

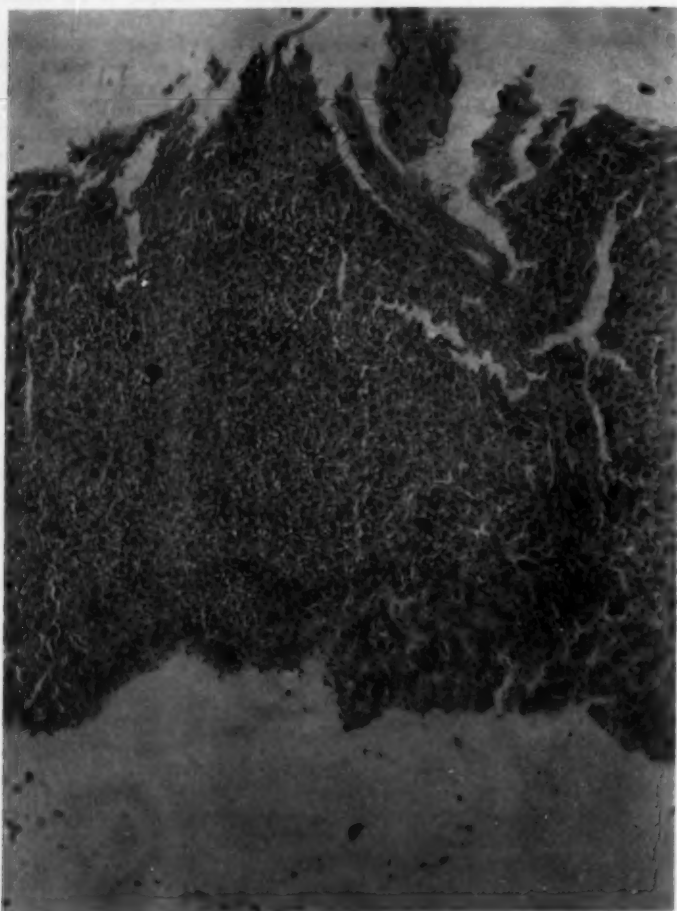


FIG. 1. Photomicrograph of liver obtained by needle biopsy 20 days after onset of clinical jaundice. There are slight bile staining of some of the liver cells and accumulations of bile in a few of the canaliculi.

that time it was considered that the methyl testosterone or the diethylstilbestrol might be implicated, but it was agreed that exploration would be undertaken if the evidence still favored the possibility of extrahepatic obstruction.

Laboratory Data (November 19): Urinalysis: Specific gravity, 1.010, 2 to 4 white blood cells per high power field; 1 plus dextrose; bile present. Hemogram: hemo-

globin, 10 gm. per 100 ml. of blood; 3.09 million red blood cells per cubic millimeter of blood; 5,500 white blood cells per cubic millimeter of blood; differential count revealed 16% eosinophils, 47% segmented polymorphonuclear leukocytes, 25% lymphocytes and 1% monocyte. Daily determinations of urine urobilinogen taken from November 19 to December 12 were negative. The Kline test was negative. The erythrocyte sedimentation rate was 45 mm. in one hour. Determination of serum bilirubin: 12.4 mg. per cent at one minute, 16 mg. per cent at 10 minutes, and 16.7 mg. per cent at 30 minutes. The icterus index was 129 units. The cephalin-cholesterol test was negative in 24 and 48 hours, and the thymol turbidity was 3 units. The prothrombin time was 100 per cent of normal. The fasting blood sugar was 47 mg. per 100 ml. of blood. The serum sodium was 303 mg. per 100 ml., the serum potassium was 20.4 mg. per 100 ml., and the serum chloride expressed as NaCl was 538 mg. per 100 ml. The icterus index was 140 units on November 24, 148 units on December 2, and 140 units on December 9. On December 9 the prothrombin time was normal, the thymol turbidity test was 4.5 units, the cephalin-cholesterol flocculation test was negative in 24 and 48 hours, the serum cholesterol was 138 mg. per 100 ml., the alkaline phosphatase was 14.5 King-Armstrong units, and the serum amylase determined by a modified Somogyi method was 43 units, which is in the normal range. An x-ray examination of the upper gastrointestinal tract made December 4 revealed no abnormality.

The patient received 10 mg. of methyl testosterone daily for 104 days. The dosage was then increased to 20 mg. daily for 116 days, after which the methyl testosterone was discontinued. During a period of 230 days the patient received 3.36 gm. of methyl testosterone. The jaundice was noted by the patient after she had been taking methyl testosterone for 178 days. She had received 2.53 gm. of the drug by this time. She continued to receive methyl testosterone for 49 days after the onset of the jaundice.

The patient was transferred to the surgical service on January 11, 1953. In addition to the medication that had been given on the medical service, she was given 10 mg. of vitamin K twice a day. During a period of five days prior to laparotomy the laboratory studies revealed essentially the picture previously reported. The alkaline phosphatase was 12.6 King-Armstrong units; serum protein was 6.00 gm. per cent; the thymol turbidity test showed 7 units, and the cephalin-cholesterol flocculation test was negative at 24 and 48 hours. Fasting blood sugar determinations ranged from 38 mg. per cent to 50 mg. per cent. The icterus index was 100 units. The prothrombin time was 96 per cent of normal. The plasma chlorides were 548 mg. per cent; the hemoglobin was reported as 14.2 gm. per 100 ml. of blood. The white cell count was 4,700 leukocytes per cubic millimeter, and the differential count revealed 12% eosinophils, 8% stab forms, 48% segmented neutrophils, 17% lymphocytes and 5% monocytes.

The patient was prepared for operation by intravenous administration of whole blood, Amigen, cevitic acid and Betalin Complex. A continuous intravenous drip of 10 mg. of ACTH over a period of 10 hours was given on the three days immediately preceding operation. ACTH was administered in the same manner and dosage for seven days after the operation. At the time of laparotomy it was noted that the liver was slightly enlarged and perhaps contained some fibrosis, but did not present the typical appearance of cirrhosis. The liver was deeply pigmented. There were a number of old fibrous adhesions between the stomach, the under surface of the liver, the duodenum and the gall-bladder. Careful exploration of the lesser peritoneal cavity revealed a small mass on the posterior wall of the stomach that was believed to be a leiomyoma or benign fibroma. The pancreas was quite soft in all portions, with no evidence of disease. It appeared to be pinker than is usually observed but did not suggest pancreatitis. An incision was made in the anterolateral portion of the common duct below the cystic duct and exploration was performed. It was

found that the probe and dilator dropped into the duodenum without meeting resistance. Exploration of the common duct and both hepatic ducts by sounds revealed no evidence of obstruction. The edge of the left lobe of the liver was selected as a site for biopsy. The patient tolerated the operative procedure very well.

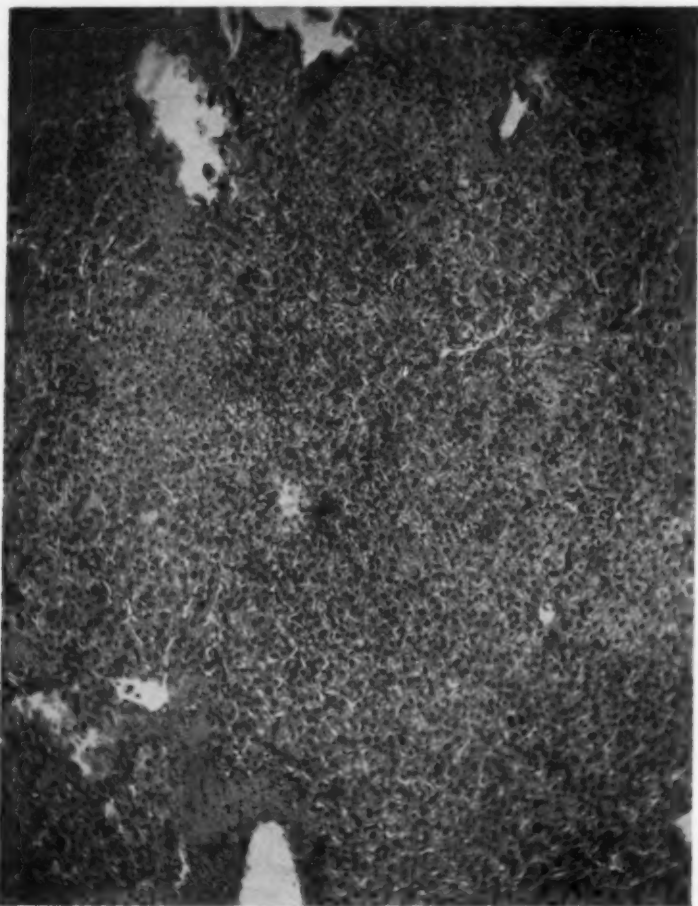


FIG. 2. Photomicrograph of liver tissue obtained by biopsy at time of laparotomy 74 days after onset of clinical jaundice. Evidence of hepatocellular damage is minimal.

The pathologist submitted the following report on the tissues: Microscopic: Section of nodule from stomach shows hyalinized calcified lymph node. Liver biopsy shows early fibrosis of portal areas. Liver cells show cloudy swelling and marked bile pigmentation. There is extensive plugging of the canaliculi. Diagnosis: Hyalinized lymph node of stomach; early portal cirrhosis; intrahepatic biliary stasis.

Figure 2 is the photomicrograph of the tissue obtained at laparotomy.

Twelve days after the operation the patient was transferred to the medical service. She was ambulatory at the time and her jaundice was clearing. One month later she was discharged from the hospital. She had improved continuously and was only mildly jaundiced. She has been visiting the out-patient department at monthly intervals, and was free of jaundice when seen on March 27, 1953. The status of the liver is being checked periodically and it is planned to re-institute methyl testosterone after the laboratory tests have indicated normal liver function for at least six months.

DISCUSSION

The appearance of the liver obtained by biopsy from a case of this type was first described by Werner, Hanger and Kritzler.² These workers noted that the lesions were confined to the central zones of the liver lobules, and that the bile canaliculi in the central zones were dilated and plugged with bile pigment. There was a moderate amount of bile pigment in some of the liver cells. Minimal liver damage was noted in the central zones. There was no inflammatory reaction in the liver lobule or in the portal area, nor was there change in the configuration of the liver lobule. The bile ducts were not dilated and contained no bile. Later in the course of the disease a second biopsy revealed the same findings plus a mild fat accumulation in some of the cells, and in some of the lobules connective tissue extended along the sinusoids in the central zones. In a few lobules a small number of lymphocytes infiltrated the areas. These findings have been confirmed by many other workers.

The mechanism of the action of methyl testosterone in producing the liver damage remains obscure. When Kinsell³ called attention to methyl testosterone jaundice in 1948 he pointed out that methyl testosterone caused marked creatine formation and excretion, and that this may occur at the expense of choline, with a decrease in the production of phospholipid and the resultant fatty infiltration of the liver. In a personal communication to Brick,⁴ Kinsell reported that there was no evidence of fatty infiltration in specimens obtained by liver biopsy. He therefore concluded that there was no substantiation of the belief that the loss of creatinine resulted in loss of labile methyl groups that are considered to be instrumental in minimizing liver damage and fatty infiltration. Wood⁵ cited the conclusions of Wilkins, Fleischmann and Howard⁶ that methyl testosterone ingestion results in increased urine output of 17-ketosteroids, and offers the possibility that an intermediate metabolic product of methyl testosterone, rather than methyl testosterone itself, may be the icterogenic factor as well as the cause of creatinuria.

The probability that the injury to the liver cells by methyl testosterone leads to disturbance of normal hydration of bile which becomes too viscid to flow through the intralobular ducts is proposed by Werner, Hanger and Kritzler.² There seems to be no reason to believe that methyl groups, per se, cause this type of jaundice.

Hypersensitivity to methyl testosterone is eliminated as the cause of the phenomenon, since it was noted by Werner and co-workers² that recurrence did not follow resumption of administration of methyl testosterone to two patients who recovered from this type of jaundice.

As shown in the photomicrograph of the liver tissue taken at the time of

operation (figure 2), and also by means of the Silverman needle (figure 1), the lesion seems to be minimal. Bile plugs are seen in the canaliculi, and a moderate amount of bile pigment occurs intracellularly, but evidence of marked liver parenchyma damage or inflammatory reaction is lacking. As noted by Werner, Hanger and Kritzer,² the absence of portal triad involvement or swelling of the bile ducts differentiates this lesion from that produced following the administration of arsphenamine. The characteristic appearance of the tissue makes liver biopsy an extremely valuable aid in the diagnosis of this disease. There is great disparity between the histopathologic picture and the clinical degree of jaundice.

Bonner and Homburger⁷ call attention to the fact that, of the 17 cases reported up to the time of their report, only two patients were female. This report adds the third female to this group. Further observations must be made before the role of sex in predisposition to development of this type of jaundice can be ascertained.

Although some writers have called this condition hepatitis, Dr. Leon Schiff⁸ objects to the application of the term, since a characteristic feature of the histopathology is the lack of inflammatory cells or other features characteristic of an inflammatory process.

SUMMARY

A case of jaundice following the administration of methyl testosterone has been reported. This is the nineteenth such case to be reported in the medical literature. Although a severe and progressive jaundice occurs, the usual laboratory tests for hepatocellular damage are negative. Complete recovery follows discontinuance of the methyl testosterone. The microscopic appearance of the material obtained by needle biopsy and by biopsy at time of laparotomy is similar to that described by Werner and co-workers, who regard it as a distinct type of lesion characterized by stasis in the bile capillaries of the central portion of the liver lobule, with no obstruction of the larger bile ducts and without much evidence of hepatocellular damage.

The mechanism of production of this type of jaundice remains obscure, but the premise that the bile is too viscid to flow through the canaliculi seems to be the most acceptable explanation yet offered.

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**SPONTANEOUS PNEUMOTHORAX COMPLICATING
PNEUMONIA ***

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THE incidence of spontaneous pneumothorax occurring as a complication of pneumonia in adults is apparently very low, since reports in the literature are sparse.^{1, 2, 3} Numerous reports of such cases in children have been recorded.^{4, 5, 6, 7} The occurrence of two cases in otherwise healthy males during an epidemic of respiratory infections seemed sufficiently uncommon to warrant this report.

CASE REPORTS

Case 1. This 21 year old white male was admitted to the hospital on February 8, 1953, complaining of pain in the right chest, anorexia and cough for three days with

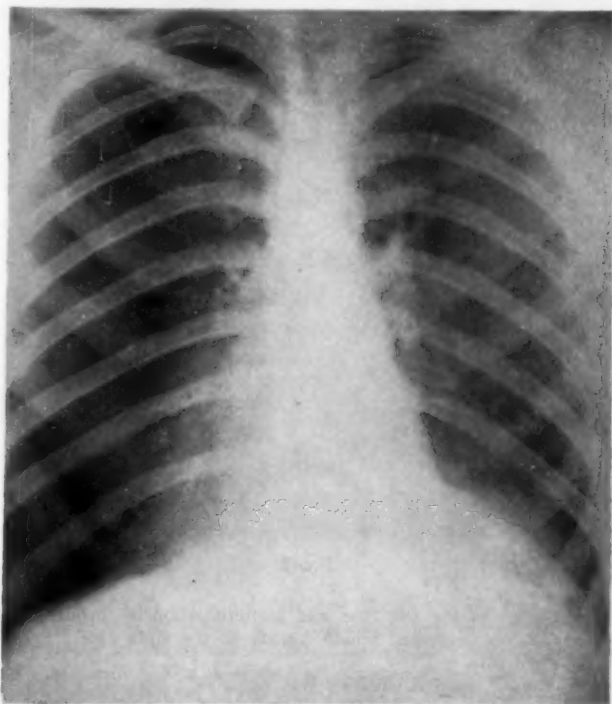


FIG. 1.

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From the Departments of Radiology and Internal Medicine, U. S. Army Hospital, Fort Leonard Wood, Missouri.

bloody sputum and increasing dyspnea in the previous two days. Chest pain became more severe on the night the patient was admitted to the hospital.

Past History: The patient had had pneumonia at the age of seven, and a questionable rheumatic fever two years previously.

Physical Examination revealed a fairly well developed, poorly nourished short white male who appeared acutely ill, apprehensive and somewhat dyspneic. His cough was productive of a blood-streaked sputum. Admission temperature was 104° F. The pharynx was moderately inflamed. Examination of the chest revealed labored breathing, with slightly less movement of the right chest. There were

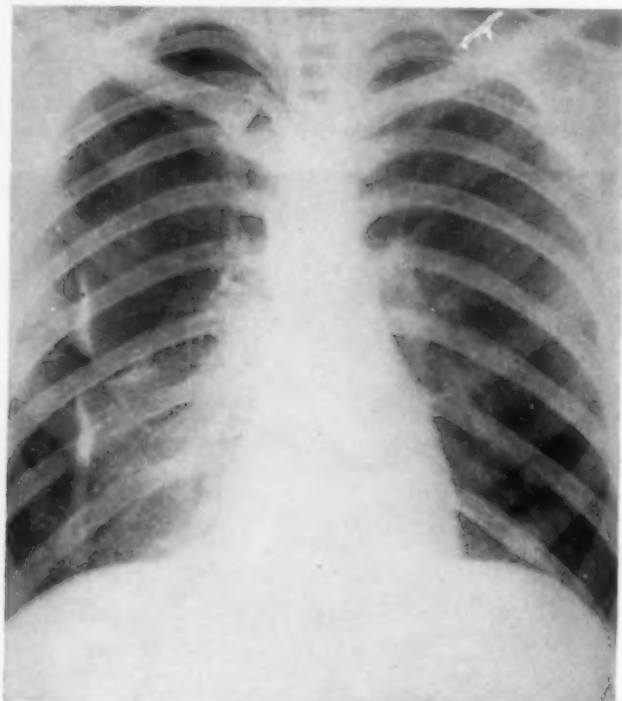


FIG. 2.

crackling moist râles at the left base and scattered rhonchi throughout the entire chest, with moderately decreased breath sounds on the right side. Percussion was painful on the right side.

Laboratory and X-Ray: Urinalysis was negative. Admission white count was 10,400; repeat white count was 3,500. Admission x-ray of the chest (figure 1) demonstrated a partial collapse of the entire right lung by a pneumothorax of approximately 40 per cent, with shift of the mediastinum to the left. There was a pneumonic consolidation at the left base, but the remainder of the lung fields was clear. Repeat x-ray on February 19 (figure 2) revealed a partial reexpansion of

the right lung. The pneumonic process at the left base had cleared. Follow-up on February 27 showed almost complete reexpansion of the right lung. The last film, done on March 11 (figure 3), demonstrated complete reexpansion of the right lung. There were no pulmonary infiltrations present.

The patient responded quickly to penicillin, bed-rest and a high caloric diet. He was afebrile after the first two days. Physical examination revealed rapid disappearance of the signs of pneumonia and gradual expansion of the right lung.

Diagnosis: Right spontaneous pneumothorax, secondary to left lower lobe pneumonia, organism undetermined.

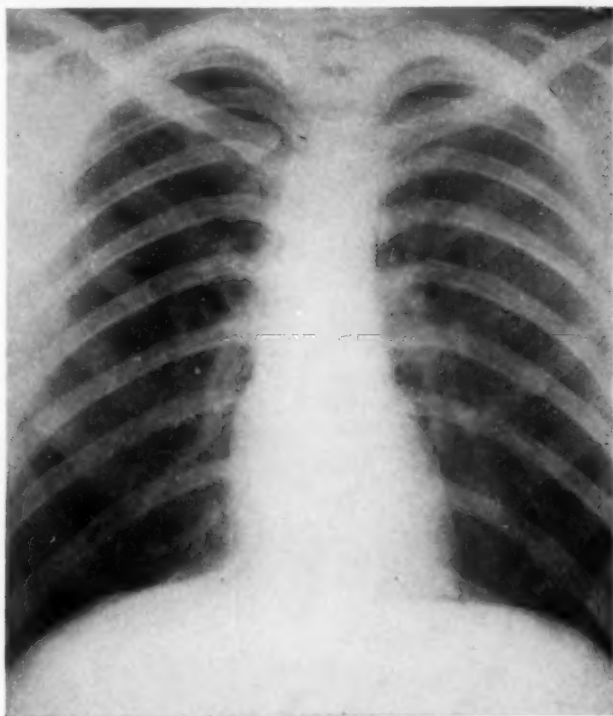


FIG. 3.

Case 2. This 22 year old white male was admitted to the hospital on February 4, 1953, with a history of having had a dry, hacking cough for two days. He had had no upper respiratory infections and no known foreign body aspiration or exposure to tuberculosis. At about 6:30 a.m. he had an acute onset of sharp pain in the right lower rib cage anterolaterally. This pain gradually went upward to beneath the right breast. As he walked to work he felt a "lump like a rock bouncing at the root of my lung." His right shoulder felt as though it was hard to move, and he had a slight pain on leaning backward. At the time of admission he had only slight pain, "like a congestion," at the hilus, but this was very mild. He had had very slight dyspnea on walking or running.

Past History revealed that he smoked one to three packs of cigarettes a day. He had had pneumonia 12 years previously, which he thought was on the right side. During the past winter he had had his first cold in seven years.

Physical Examination: Temperature, 101° F.; pulse, 104; blood pressure, 130/80 mm. of Hg; respirations, 20. The patient was in no acute distress. There was no cyanosis, dyspnea or apparent pain. The right chest appeared fixed and was hyperresonant, with absent breath sounds. The left chest was normal. Heart examination revealed the point of maximal impulse and left heart border to be 3 cm. outside the left midclavicular line; the right border was deep to the midsternum; heart sounds

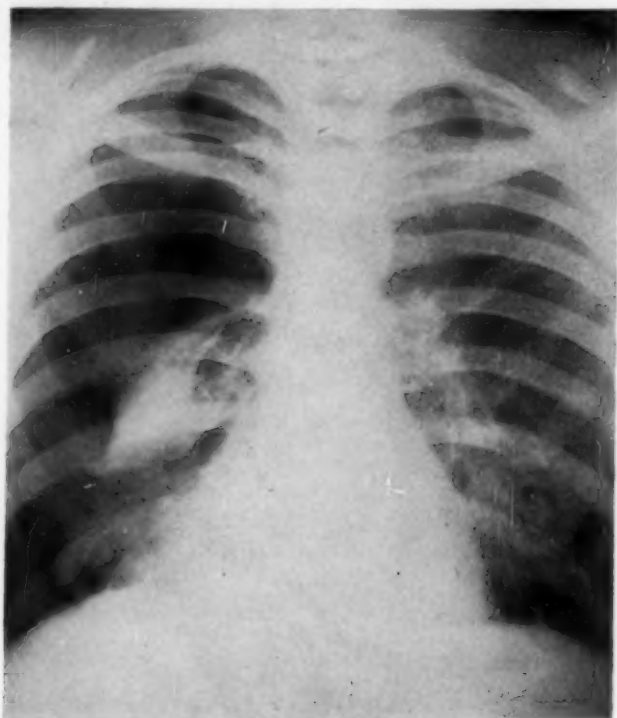


FIG. 4.

were distant, and there were no murmurs. The remainder of the physical examination was entirely negative.

Laboratory and X-Ray: Urinalysis and serologic tests for syphilis were negative. White blood count was 12,250, with 73 per cent polys, 24 per cent lymphocytes, 3 per cent monocytes; hemoglobin, 15.5 gm. Repeat white count was 10,750. The initial x-ray (figure 4) revealed a pneumothorax of the right lung, with complete collapse of the entire lung. The lung expanded rather rapidly, and the pneumothorax gradually decreased (figure 5). As the lung expanded a patchy infiltration was seen in the right pericardiac region (figure 6); it was felt that this was a primary

atypical pneumonia which was responsible for the pneumothorax. Serial x-rays showed gradual resolution of the pneumonic process and reëxpansion of the right lung (figure 7), with normal x-ray findings after 33 days.

Course in Hospital and Therapy: The patient was treated with absolute bed-rest, penicillin, cough mixture and symptomatic care, and no smoking. He was completely afebrile after the third hospital day and was asymptomatic throughout his stay in the hospital. As the lung reëxpanded the breath sounds in the right side of the chest increased and finally equalled those of the left chest. A few râles in the right base, the only evidence of pneumonia, were of very brief duration. X-ray of the chest on March 9 showed complete reëxpansion and complete clearing of the lung.

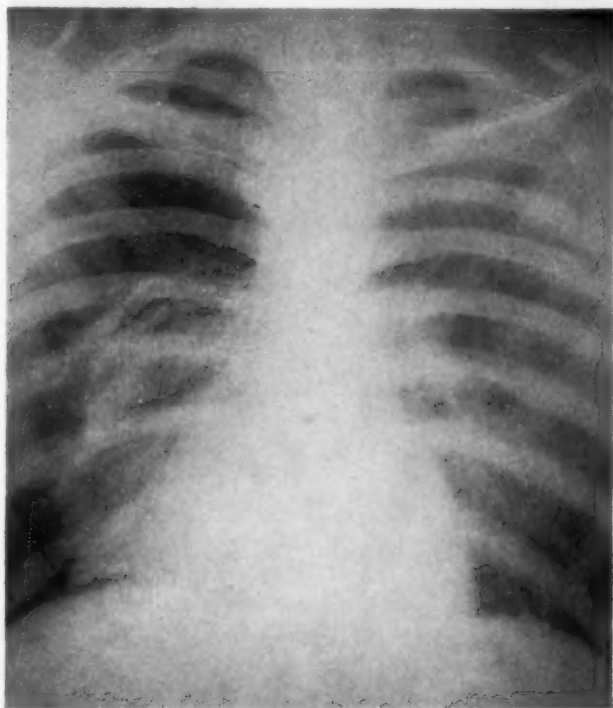


FIG. 5.

Diagnosis: Right spontaneous pneumothorax, secondary to primary atypical pneumonia, right base.

DISCUSSION

Pathogenesis: We agree that the pneumothorax in these cases can be ascribed to the rupture of overdistended alveoli as a result of severe coughing.⁸ Rubin² feels that the reasons for a low incidence of pneumothorax complicating lung infections in adults are the development of pleurisy and the lack of localized pulmonary overdistention.

Incidence: A review of the literature revealed very few reported cases in adults. Thomas⁸ published seven cases in 1941, prior to antibiotic therapy. Glendy¹ describes only one case of pneumothorax in 150 patients with primary atypical pneumonia. In a study of 200 cases of atypical pneumonia, Levitt and Hamburg⁹ reported no patients with pneumothorax. It is interesting that there is little emphasis on complicating pneumothorax in pneumonias in various texts,^{10, 11} and no mention of it in others.^{12, 13}

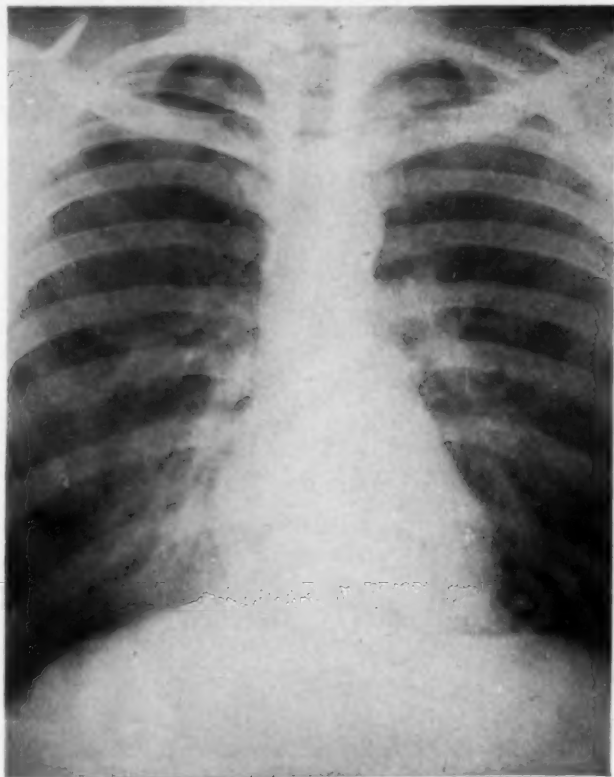


FIG. 6.

CONCLUSIONS

1. Pneumothorax should be suspected whenever dyspnea out of proportion to the pneumonic involvement is observed.
2. On the other hand, atypical physical findings of a pneumothorax in a febrile patient should suggest the possibility of an underlying pneumonia.
3. Treatment of the underlying pneumonia with antibiotics, bed-rest and supportive therapy is ordinarily sufficient in these cases, without utilizing withdrawal of air from the thoracic cavity.

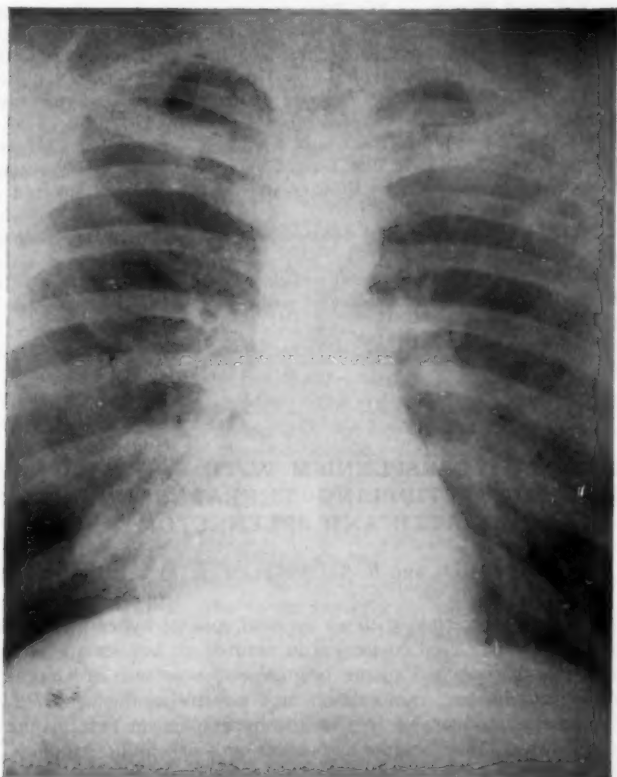


FIG. 7.

4. Complicating pneumothorax apparently did not alter the course of the pneumonia.

SUMMARY

Two cases pneumothorax complicating pneumonia in young adults are reported.

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CONGENITAL HYPERSPLENISM WITH PANCYTOPENIA AND BASOPHILIC STIPPLING: THERAPEUTIC FAILURE OF ACTH AND SPLENECTOMY *

By E. SHANBROM, M.D., and R. L. WESTERMAN, M.D., *Ancon, Canal Zone*

THIS report is concerned with an unusual case of hypersplenism which we believe should be considered congenital in nature. It is a unique study because this patient was born in a Panama hospital and was seen at Gorgas Hospital for all subsequent medical examinations and treatments during her 13 years of life. This case is unique also in that the hypersplenism first manifested itself by an anemia which later became associated with basophilic stippling, thrombocytopenia and neutropenia. Because of these unusual features the case is presented in detail.

CASE REPORT

A 13 year old white girl was admitted to Gorgas Hospital on August 24, 1952, with the history of generalized crampy abdominal pain of five days' duration, with the pain most severe in the right lower quadrant. She had been vacationing in the interior of Panama several days prior to admission. During this period she had had anorexia and had been apathetic and listless. On the day of admission she was nauseated, had an episode of coffee-ground emesis, and passed four watery, blood-tinged stools. Three years previously she had had a similar episode, consisting only of abdominal pain. This was diagnosed as appendicitis, but no operation was performed.

There had been eight previous hospital admissions:

She was born on March 3, 1939, in Santo Tomas Hospital, Panama City. The birth record is nonrevealing and no gross physical abnormalities were noted at that time.

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From the Medical Service, Gorgas Hospital, Ancon, Canal Zone.

The child's parents were divorced and the child continued to live with the father. As a result we have not been able to obtain an accurate history of her first year of life.

She was admitted to Gorgas Hospital, Ancon, Canal Zone, for the first time in August, 1940 (at the age of one and one-half years), because of anemia and malnutrition. She had had a cold two weeks prior to admission from which she made a poor recovery, remaining listless and fretful. She appeared to be chronically ill. The spleen was palpable two fingerbreadths below the costal margin. The red blood cell count ranged between 2,200,000 and 3,000,000, with the hemoglobin ranging between 48 per cent and 55 per cent. The white cell count fluctuated between 8,200 and 10,800, with one single rise to 19,650, occurring during an episode of acute tracheobronchitis which developed during her hospitalization. Numerous malaria smears were made and all were negative. No explanation for the splenomegaly was found.

She was next admitted in March, 1943, because of recurrent colds with recently associated weakness and listlessness. The spleen was felt 3 cm. below the costal margin. The red blood cell count was 3,520,000 and the hemoglobin was 65 per cent. The white cell count ranged between 5,500 and 7,000.

In January, 1944, she was admitted for three days for a tonsillectomy. It was not recorded that the spleen was palpable. The red blood cell count was 3,500,000, with the hemoglobin 65 per cent. The white cell count was 7,350. Two days after discharge she was re-admitted for six days because of infection of the tonsillar beds. The white cell count was now 4,500.

In September, 1944, she was admitted because of a simple transverse supracondylar fracture of the humerus. No note was made regarding the abdominal examination. The red blood cell count was 3,930,000, with the hemoglobin 78 per cent. The white cell count ranged between 8,000 and 9,500.

In January, 1946, she was admitted because of symptoms for one week of a "cold" with headache and drowsiness. The spleen was enlarged to the iliac crest. Studies to explain this included an adrenalin test for malaria parasites, hemogram, red cell fragility test, chest x-ray and an intravenous pyelogram; all were normal. No diagnosis was made. The upper respiratory infection subsided spontaneously. The red cell count ranged between 3,550,000 and 3,940,000; the hemoglobin was 70 per cent. The white cell count ranged between 4,850 and 6,000. A single determination of the platelets was 116,500.

In October, 1947, she was admitted because of dizzy spells of two months' duration, with associated nonspecific headaches. On several occasions there had been vertigo, and two days prior to admission she had had abdominal pain. The spleen was again noted to be at the iliac crest. The red blood cell count was 3,760,000, with the hemoglobin 75 per cent. The white cell count was 6,000, with 44 polymorphonuclear cells and 56 lymphocytes. Two adrenalin tests for malaria parasites were negative. The spinal fluid, nonprotein nitrogen, fasting blood sugar and basal metabolic rate were all normal. She was asymptomatic during hospitalization, and it was felt that her symptoms were on a psychogenic basis.

In June, 1949, she was admitted because of crampy, aching lower abdominal pain of one day's duration, with essentially negative physical findings except the previously noted splenomegaly extending to the iliac crest. Her pain seemed to be of an intermittent nature and subsided spontaneously in two days. The red cell count ranged from 4,200,000 to 4,700,000, with a hemoglobin of 78 per cent to 84 per cent. The white cell count was 4,200, with 66 polymorphonuclear cells and 34 lymphocytes. A hemogram was normal. The platelets were 127,500.

Her out-patient clinic record during this period revealed that she had sustained the usual minor injuries of childhood. She seemed to be particularly prone to the development of skin lesions, especially impetigo, and she had had numerous upper respiratory infections. She had been seen for two months in 1947 on an out-patient

basis by the hospital psychiatrist, who had been impressed by her general apathy, listlessness and dizzy spells.

There is no known history of anemia, jaundice or blood dyscrasias in other members of the family.

The system review for the present admission was noncontributory, although it was noted that she had not yet menstruated.

During the present admission physical examination was essentially negative except for splenomegaly of three to four fingerbreadths and a sense of resistance and tenderness in the right lower quadrant. She was admitted for observation. She continued to be nauseated, and later in the day she again had coffee-ground emesis with a black watery stool, both of which gave a positive test for occult blood. She was reexamined at this time and it was noted that there was a suggestive tinge of icterus to the sclerae; however, a serum bilirubin was not done until two days later, at which time it was 1.2 mg. per cent with a 3 plus cephalin flocculation reaction in 48 hours and a plus-minus van den Bergh reaction. The initial red blood count was 3,510,000, with 9.0 gm. of hemoglobin. The white cell count was 6,150, with 60% polymorphonuclear cells and 40% lymphocytes. On the third day the nurse reported that the patient seemed to have a cold. Her abdominal complaints in the meantime had subsided spontaneously. She was transferred to the Medical Service on the fifth day after the finding of a platelet count of 64,800, leukopenia of 2,500, with 28% polymorphonuclear cells, 66% lymphocytes, 6% eosinophils and basophilic stippling of the red blood cells. The prothrombin, bleeding and clotting times were normal.

Other laboratory findings were: clot retraction which began at seven and one-half hours and was poor at the end of 24 hours; sickle cell preparation negative; Rumpel-Leede test negative; red cell fragility test showing hemolysis beginning in 0.38 per cent and complete in 0.30 per cent solutions of sodium chloride; mean corpuscular volume, 82 cubic microns; mean corpuscular hemoglobin, 27 micro-micrograms; mean corpuscular hemoglobin concentration, 32.7 per cent; reticulocyte count, 0.4 per cent. A needle biopsy of the bone marrow showed basophilia and basophilic stippling of the red blood cells with the erythrocyte-granulocyte ratio 1.4:1; no spherocytes or other abnormal cellular forms were noted. Skull x-rays for vertical striations were negative. The chest x-ray was negative. Skeletal x-rays did not reveal lines of heavy metal accumulation. Several urines were negative for bile. A urinary test for lead excretion was negative. A fasting gastric analysis showed 48° of free and 68° of total acid. An upper gastrointestinal series revealed only heavy mucosal folds in the fundus of the stomach and gastrointestinal hypermotility. Stool trypsin activity was normal. Bromsulfalein retention was 6 per cent at 45 minutes. The serologic tests for syphilis and heterophil tests were negative.

By the eleventh day the clinical icterus had subsided and the serum bilirubin was 0.25 mg. per cent; the cephalin flocculation was 1 plus, with the van den Bergh negative. However, the cold hemagglutinin test was positive in a dilution of 1:256, and three days later was negative. Control blood counts were taken that day, and the following day an adrenalin test was performed. There was a prompt but transient rise in the red and white cell counts, with an irregular platelet response.

On the eighteenth day an excision biopsy of the sternal bone marrow was performed and showed a hyperplastic marrow. The following day the patient complained of mild abdominal distress with nausea, weakness and dizziness. Clinically she again had a minimal icteric tinge, and the serum bilirubin was 2.0 mg. per cent, with the cephalin flocculation 4 plus in 48 hours. The van den Bergh reaction was negative, and the cold hemagglutinins were positive in a 1:1024 dilution.

On the nineteenth day a course of ACTH therapy was begun, consisting of 20 mg. in 2,000 c.c. of 5 per cent glucose intravenously over a 24 hour period for seven days. On the fourth day of therapy the serum bilirubin was 0.25 mg. per cent and the cold hemagglutinins were negative, but the cephalin flocculation was still 4 plus.

Daily blood counts during this interval showed no striking response and only a slight rise in the white blood count to suggest any beneficial effect.

There continued to be some rise in the white count for one week after therapy, but at the end of two weeks it had returned to pretreatment levels. There also seemed to be some regression in splenic size but this gain had also disappeared at the end of a month. Five weeks after treatment the patient was again experiencing dizzy spells, headaches and general malaise. During a clinic visit seven weeks later icterus was again noted, and was confirmed by finding the bilirubin 2.8 mg. per cent with a 2 plus cephalin flocculation.

In view of an only temporary response to medical management the patient was admitted at the end of November for splenectomy. Physical examination was as previously noted and the hematologic findings were as before, with the exception of a higher red blood count and hemoglobin (4,300,000 and 11.0 gm.). At surgery the vascular supply of the spleen was noted to be extremely well developed. The patient received 1,000 c.c. of whole blood that day. She tolerated the procedure well and had an uneventful recovery except for symptoms and signs of another hemolytic episode the day of and the day after surgery. Her first menses began one week after surgery. There was a gradual rise in all cellular elements and she was discharged on the eleventh postoperative day, at which time her red cell count was 4,130,000, with 12.5 gm. of hemoglobin. The white cell count was 7,600 and the platelet count 300,000 to 400,000. The reticulocyte count was 0.1 per cent.

TABLE I

	RBC	WBC	Platelet
Preadrenalin Test	2,250,000	2,000	37,000
Adrenalin Test Peak	3,770,000	15,650	75,680
Pre-ACTH	3,120,000	2,100	—
ACTH Peak	3,280,000	3,900	—
Presurgery	4,610,000	2,750	147,620
Postoperative 1 day	3,940,000	8,500	240,000
1 week	4,200,000	8,450	1,512,000
1 month	3,500,000	11,500	189,000
2 months	4,250,000	9,900	110,500
4 months	3,670,000	7,250	513,800
6 months	3,400,000	8,800	512,000

The pathologists reported the spleen as weighing 353 gm. The germinal centers were decreased in number and size. The sinusoids were dilated and showed a slight fibrosis of their walls.

The patient was followed monthly in the medical clinic. She maintained the elevation of all cellular elements and felt well. Her father and friends felt that she had become more alert, more energetic and happier. She no longer had episodes of "dizzy spells." She continued to have normal menstrual periods. On April 16, 1953, five months following her splenectomy, she appeared to have minimal icterus of her sclerae and, when asked, replied that she had had a very slight "dizzy spell" the previous week, but that it had not been so severe as in the past. Laboratory findings revealed: red blood count, 3,500,000; hemoglobin, 11.5 gm.; white blood count, 9,600, with 46% polymorphonuclear cells and 54% lymphocytes; platelets, 379,480; icterus index, 11; van den Bergh, negative; quantitative serum bilirubin, 1.3 mg.; cephalin flocculation, negative. One month later the icterus had completely disappeared and blood counts were: red blood cells, 3,880,000; hemoglobin, 12.5 gm.; white blood cells, 10,200, with 74% polymorphonuclear cells, 20% lymphocytes, 2% monocytes and 4% eosinophils. Up to the time of writing (six months after splenec-

tony), several minor dizzy spells have occurred but the blood picture is essentially the same. The patient continues to feel considerably improved.

DISCUSSION

Although this case readily fulfills all the criteria of congenital splenic pan-hematopenia, there are some unusual features which need further comment. It is remarkable to note the similarity between our case and the first recorded case of congenital splenic pancytopenia reported in the literature by Doan and Wright in the first issue of *Blood* (1946).¹

That gastrointestinal hemorrhage was the presenting symptom for this present admission in our patient was probably due to the combination of a low platelet count and a severe gastroenteritis which she developed while visiting in the interior of Panama.

The marked basophilic stippling present during a hemolytic episode in our patient, together with the clinical picture of a severe gastrointestinal disorder and bizarre central nervous system involvement, suggested that lead poisoning might be the underlying pathology. Subsequent studies failed to support this diagnosis. The significance of the stippling is not clear, and this case demonstrates well the fact that this abnormality of erythrocytes is not indicative solely of lead poisoning. We have recently seen a case of marked basophilic stippling in acute blood loss associated with postpartum hemorrhage. Stippling of red cells has been reported in thalassemia.² The presence of basophilic stippling has been described by Haden³ in two families with hereditary hemolytic anemias, and a case of congenital hemolytic anemia with this same abnormality of the red cells was recently reported by Feinberg and Watson.⁴ Stippling has been reported in the blood of normal persons.⁵ The mechanism by which stippling occurs is not well understood. It has been suggested that the phenomenon may occur as a result of injury to the cell membrane, and the basophilic substance of young erythrocytes is then precipitated by stains.⁶

The symptom complex by which a hemolytic episode manifests itself in our patient is of special interest. With the exception of the vague abdominal pain that occurred on a few occasions, hemolysis was always associated with symptoms of mental aberration—dizziness, listlessness, fretfulness, headaches and apathy. As a matter of fact, her personality change was sufficient to require the services of a psychiatrist, who attributed her findings to a childhood adjustment problem. That many hemolytic episodes were accompanied by minor upper respiratory infections suggested a causal relationship in that these "stress" situations may have been sufficient to incite hemolysis; on the other hand, her leukopenic state may well have increased her susceptibility to these recurrent infections, although we have no evidence of the existence of leukopenia before the age of five.

The hemolytic episode following splenectomy deserves comment. Most likely this resulted from manipulation of the spleen during operation, but other factors may have contributed. These patients classically tolerate transfusions poorly, and our patient had received two pints of blood. Finally, surgery itself was a "stress" situation sufficient to precipitate a hemolytic episode.

The presence of cold agglutinins during an "attack" and their disappearance are highly presumptive evidence that her anemia was caused by an abnormal antibody. It is of interest that, although cold agglutinins were positive in a titer of 1:256 11 days following her gastrointestinal bleeding, they rapidly became

negative during ACTH therapy four days after the onset of another hemolytic episode. The initial titer in this instance had been 1:1024.

The possibility that accessory spleens may be the reason for the failure of splenectomy to produce a cure in this case must be considered, since a complete exploration of the abdomen was not done during surgery due to technical difficulties.

The question of liver disease is important here. Although a liver biopsy was not done at surgery as we had requested, one of us (E. S.) was present during the operation and observed that the liver appeared somewhat pale and fibrotic; this was also observed and commented on by the surgical team. The persistence of a positive cephalin flocculation test is in favor of primary disease of the liver, while the normal bromsulfalein test is against it. The subject of hemolytic anemia associated with liver disease has been well covered by Hyman and Southworth.⁷ They point out the unsatisfactory response to splenectomy that is to be expected in those cases in which the liver is severely damaged. They also cite the theories of hepatic damage resulting from repeated hemolytic episodes. In our case the cephalin flocculation tests were increased to maximum during hemolysis but returned to a 1 plus or 2 plus during a remission. We do feel that there is much good evidence that there is present in this case a primary or congenital hypersplenic state; and therefore the liver changes that exist may well be secondary to hemosiderosis which results from repeated hemolytic episodes. Nevertheless, we feel it important to emphasize that this is a case of hypersplenism with liver disease that has not been cured by splenectomy. As more cases are studied it may become evident that a liver biopsy should be a prerequisite to splenectomy for certain of the hypersplenic states.

SUMMARY

1. A case of congenital hypersplenism with pancytopenia is presented. An unusual feature of the blood picture is the accompanying basophilic stippling.

2. The prominence of mental disturbances as presenting manifestations of hemolytic episodes in this patient is stressed.

3. ACTH and splenectomy, although capable of modifying hemolytic activity in this case, did not produce a cure.

4. The question of liver disease in this patient and its association with other cases of hemolytic anemia are discussed.

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POTASSIUM INTOXICATION PRESUMABLY DUE TO ACUTE FUNCTIONAL ADRENOCORTICAL INSUFFICIENCY *

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THE syndrome of potassium intoxication, well documented in chronic and acute renal disease¹⁻⁴ and in untreated, adrenalectomized dogs,⁵⁻⁸ has rarely been recognized clinically in adrenal insufficiency. It has been suggested that death in Addison's disease may be related to such abnormalities in serum potassium concentration.^{5,9} In this case the onset was typical of potassium intoxication; in view of the response to therapy and the subsequent course, it is presumed to be one of acute functional adrenocortical insufficiency.

CASE REPORT

A 42 year old white female was admitted to the hospital with the history of recurrent episodes of chills, fever, right upper quadrant pain, icterus, dark urine and light stools over a four year period. Gall-bladder x-ray examinations had been reported to show a "nonfunctioning gall-bladder."

She had been hospitalized here four years earlier because of thyrotoxicosis, for which partial thyroidectomy was done. During this admission abdominal exploration was also done because of a right upper quadrant mass which proved to be a multilocular hepatic cyst, which was excised. One year later the patient was hospitalized again because of amebic colitis, recurrence of right upper quadrant pain and jaundice. Despite adequate anti-amebic therapy pain and jaundice persisted, and surgery was recommended but refused.

Physical Examination: Blood pressure, 110/70 mm. of Hg; temperature, 98° F.; pulse, 96. The skin and mucous membranes were icteric. The heart and lungs were within normal limits. The liver was felt 7 cm. below the right costal margin in the midclavicular line and was hard and nodular. The spleen was also palpated 3 cm. below the left costal margin.

Laboratory Data: The urine was positive and the stool negative for bile. Hemogram revealed a hemoglobin of 14.5 gm. and a white blood count of 6,800, with a normal differential count. Blood chemical tests included: blood urea nitrogen, 11 mg. per cent; fasting blood sugar, 92 mg. per cent; albumin, 3.8; globulin, 5.3 gm.; bilirubin, 4.5 mg.; thymol turbidity, 4.5 units; cephalin flocculation, 1 plus at 48 hours; cholesterol, 304 mg. per cent; prothrombin time, 11.5 sec., with a control of 12.0 sec. An electrocardiogram revealed no significant abnormalities. Chest film was normal, but upper gastrointestinal x-rays showed a questionable duodenal ulcer. Skull films revealed a normal sella.

Hospital Course: On the seventh hospital day, abdominal exploration was done and a polypoid cystadenoma of the left hepatic duct found and excised. The common duct was drained by T-tube. The postoperative course was uneventful until the thirteenth day. That morning the patient complained of weakness and refused lunch; at four o'clock she seemed better; supper was declined, however, and shortly thereafter she complained of extreme weakness and appeared confused. She was sweating profusely and her voice was quite weak. The skin was cold, with poor turgor; the extremities were flaccid, and respiration was shallow. Blood pressure was unobtainable, and the radial pulses were not palpable. The lungs were clear but the heart

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was small to percussion. Heart sounds were faint, with the character of a soft, distant whisper; the rate was 68 and the rhythm grossly irregular. The abdomen was not tender, but no peristaltic sounds were audible. Deep tendon reflexes were absent.

Electrocardiogram (figure 1) revealed a grossly irregular rhythm with absent P-waves, markedly widened QRS complex, and obliteration of S-T segments in the QRS complex. It was felt that the patient had acute adrenocortical insufficiency and treatment was immediately instituted, the patient receiving 1,000 c.c. normal saline, 25 c.c. 25 per cent human serum albumin, 65 c.c. aqueous adrenal cortical extract (ACE) intravenously and 10 c.c. intramuscularly, and 15 mg. desoxycorticosterone

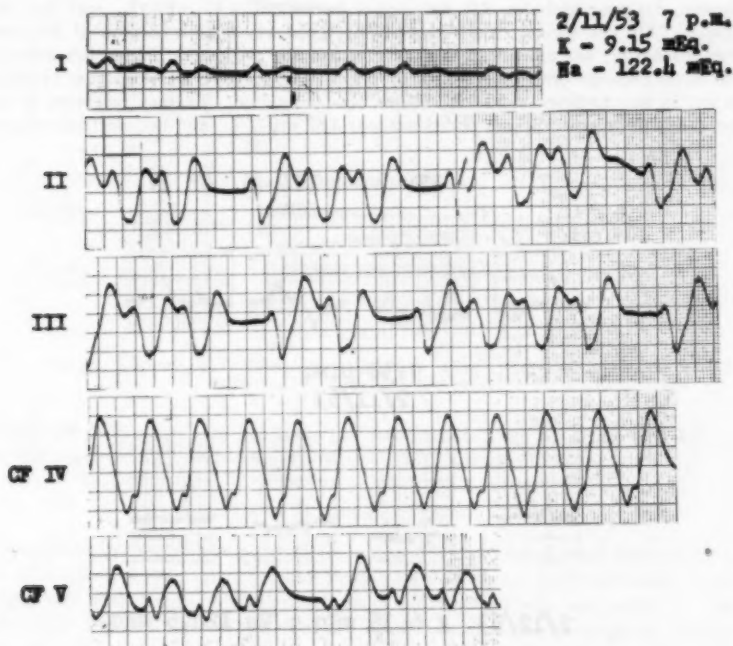


FIG. 1. Electrocardiogram taken during crisis and before institution of therapy. No P-waves are identified, there is extreme broadening of the QRS complex, and the rhythm is markedly irregular except in Lead CF IV. The broad QRS complex and the regular rhythm in this lead are quite suggestive of ventricular tachycardia.

acetate intramuscularly within the first hour. At 8 p.m. the blood pressure was 88/30 mm. of Hg, skin turgor had improved, and the patient was less confused. ACE, 5 c.c. intramuscularly each hour, was then started. At 9 p.m. blood pressure was 120/80 mm. of Hg, peristaltic sounds could be heard, the deep tendon reflexes had returned, and the patient was quite rational. Repeat electrocardiogram (figure 2) revealed a P-R interval of 0.22 sec., QRS complex of 0.10 sec., return of the S-T segment to the isoelectric line, and peaking of T-waves in Lead IV. Serum potassium and sodium, drawn at the onset, were then reported as 9.15 and 122 mEq./L., respectively. The following day cortisone, 200 mg., DOCA 5 mg., and corticotropin, 60

mg., daily, were started and ACE was discontinued. Cortisone was gradually reduced in dosage and finally discontinued after an 18 day course. Laboratory data and treatment are shown graphically in figure 3.

Six days before the patient was discharged all therapy except sodium chloride was stopped. With cessation of therapy hyperglycemia and glycosuria, which had developed, disappeared, and small bilateral pleural effusions resorbed.

Since discharge the patient has been seen on three occasions in the out-patient clinic. At her first visit, 10 days after discharge, she was doing well, though peripheral edema on standing had been noted. Icterus had disappeared and the liver had receded somewhat in size. The blood pressure was 110/76 mm. of Hg; serum albumin, 3.6 gm.; globulin, 2.9 gm.; serum potassium, 4.45 mEq./L., and Na, 142.9 mEq./L. On her second return visit she weighed 140 pounds, a gain of 30 pounds since discharge; her appetite was excellent, and she no longer limited her activities. The blood pressure was 104/76 mm. of Hg, the lungs were clear and the heart was normal in size to percussion. No edema was detectable. Further recession in liver size had taken place. Serum potassium was 4.57 mEq./L., and her electrocardiogram

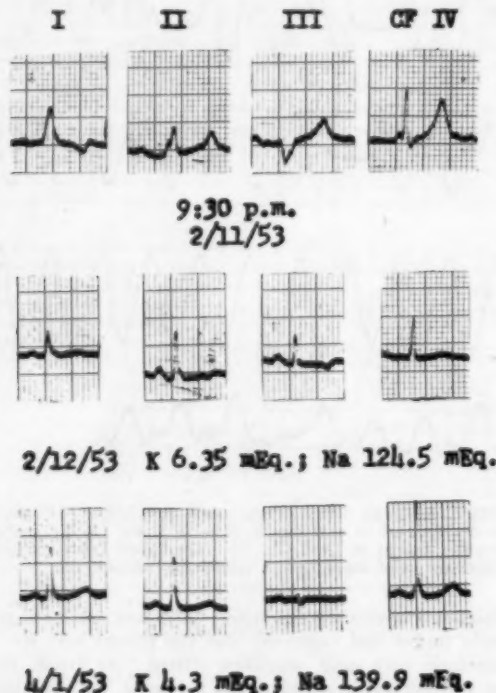


Fig. 2. Electrocardiograms after the institution of therapy. The P-R interval is prolonged and T_1 is "peaked" in the 9:30 p.m. tracing. The short P-R interval and the P-wave configuration in IV suggest a transient run of nodal rhythm. Electrocardiogram taken the following morning reveals a normal P-R interval, shortening of the ventricular conduction time and decreased voltage in Lead IV despite persistent hyperkalemia. The final tracing is essentially within normal limits.

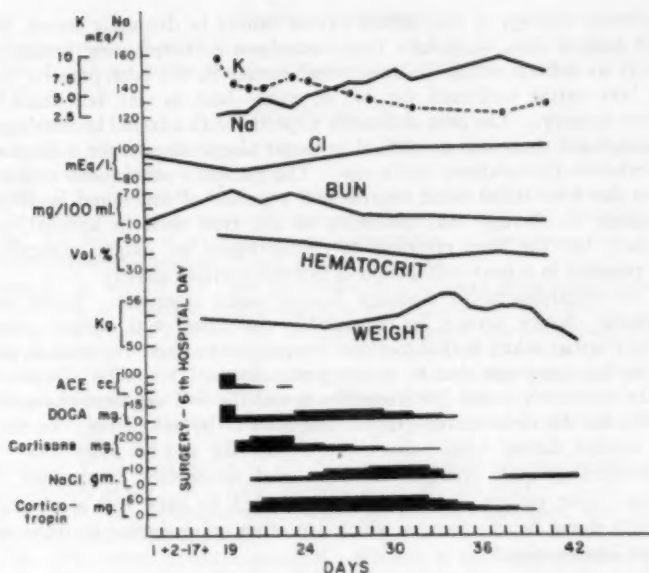


FIG. 3. Clinical data during hospitalization shown graphically. Crisis occurred on the nineteenth day.

had returned to normal. On her last visit, two months after her crisis, she had no complaints, and no abnormalities were noted on physical examination.

DISCUSSION

Potassium intoxication is generally associated with chronic renal disease, acute renal shutdown, severe intravascular hemolysis and shock with extensive tissue damage, and with the pretreatment phase of diabetic acidosis and coma.¹⁰ The diagnosis of adrenal cortical insufficiency in this case rests primarily on the absence of findings suggestive of these diseases. Hyperkalemia is commonly a consequence of renal disease, with diminished urine flow or anuria and tissue breakdown with accumulation of potassium in the serum. Massive hemolysis of erythrocytes could conceivably produce such a clinical picture, while prolonged shock may be accompanied by an elevated serum potassium, presumably attributable to tissue destruction and liberation of cellular potassium.

In reviewing this case, no history of renal disease could be found, and urinary output had been adequate until the day of crisis. The presence of a T-tube in the common duct had also provided a route for potassium excretion. Finally, the response to therapy was that typically found in acute adrenal insufficiency. In salt-losing nephritis, which may mimic it clinically, the renal tubule is apparently unable to respond to DOCA.¹ Likewise, no evidence incriminating hemolysis can be adduced, and shock sufficient to produce this degree of potassium intoxication would probably be of longer duration.

The precise etiology of this patient's crisis cannot be definitely stated, though continued sodium loss via T-tube may have been a contributing factor. Certainly such an episode would be anticipated earlier in the postoperative course. She had been eating well until the day of crisis—had, in fact, felt much better than before surgery. The pain ordinarily expected with adrenal hemorrhage was not present,¹² and there was no clinical or bacteriologic support for a diagnosis of the Waterhouse-Friderichsen syndrome. The patient's subsequent course suggests that this near-lethal event represented a period of functional insufficiency. Her response to therapy was distinctly of the type seen in adrenal cortical insufficiency, but the later response to corticotropin, as judged clinically, has perhaps resulted in a near-restoration of normal cortical activity.

The electrocardiographic findings deserve some comment. While electrocardiographic change cannot be dependably correlated with serum potassium levels, the tracings taken in this case are comparable to those reported in patients with a similar syndrome due to severe renal disease.^{1, 3, 4} The absence of P-waves, the extremely broad QRS complexes and the S-T segment changes fulfill the criteria for the electrocardiographic diagnosis of hyperkalemia. In the eight patients studied during Addisonian crisis, Somerville and his associates¹³ found no electrocardiographic changes in three and nonspecific alterations in the remainder. One patient, in extremis, was noted to have had a tracing suggestive of a dying heart, changes which are often quite similar to those seen in potassium intoxication.⁴

While apparently rare in humans, similar episodes have been reported in adrenalectomized animals. Hastings⁵ reported marked increases in serum potassium within 48 hours of completion of bilateral adrenalectomy in dogs, and suggested that this finding "may be of importance in . . . understanding the cause of death" following functional or anatomic adrenal cortical failure. Winkler and his associates⁶ confirmed this and recorded electrocardiograms characteristic of potassium intoxication. Other workers^{7, 8} have also confirmed these observations. This syndrome as a manifestation of adrenal cortical insufficiency probably is more common than is generally appreciated. Recently a somewhat similar case¹⁴ in an adult has been reported, though the onset of symptoms was more gradual and the most striking electrocardiographic change was peaking of the T-waves. Kyle and Knop,¹⁵ however, have described a case of adrenocortical insufficiency in an infant whose electrocardiogram showed changes quite suggestive of cor mortem. At autopsy there was nearly complete involution of the zona reticularis, and a definable zona glomerulosa could not be found. Hopper and his associates¹⁶ have also observed a patient with potassium intoxication (serum potassium—9.0 mEq./L.) which developed following transurethral prostatic resection. Acute renal tubular necrosis was found at autopsy, and the adrenals "were described as exhausted," with "partial necrosis" of one gland.

SUMMARY

A case is reported of potassium poisoning presumably due to acute adrenocortical insufficiency of functional origin. It is suggested that this syndrome is perhaps more common than is generally appreciated.

ACKNOWLEDGMENTS

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**CHARCOT'S INTERMITTENT FEVER OF TWO YEARS'
DURATION DUE TO CARCINOMA OF THE
AMPULLA OF VATER***

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THE hepatic intermittent fever of Charcot is due to recurrent biliary obstruction with secondary infection, and is characterized by recurrent attacks of chills, fever and sweats. Jaundice is variable and may deepen after each paroxysm.

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Abdominal pain, which is sometimes severe and colicky, is frequently absent. As a rule there is no progressive deterioration of health, but, during the intervals between the attacks, the patient is usually asymptomatic and able to carry on his activities without difficulty. Fevers may recur daily or may be separated by intervals of weeks.

A stone in the common bile duct or ampulla of Vater with chronic infective cholangitis secondary to the intermittent biliary obstruction was pointed out by Osler¹ in 1897 as a frequent cause of this clinical picture. Other causes which may give rise to this type of fever are carcinoma of the pancreas or bile ducts, strictures of the bile ducts, cholecystitis, and inflammatory changes at the entrance of the cystic duct in chronic cholecystitis.² Christian³ describes the usual pathologic findings of dilatation of the common duct and hepatic branches. The gall-bladder may be enlarged. The mucous membrane of the ducts is usually smooth and clear, and the contents consist of a thin, slightly turbid, bile-stained mucus.

The case to be presented had Charcot's intermittent fever for two years, at the end of which time a small carcinoma of the ampulla of Vater was found at laparotomy. It is felt that this case is unusual because of the absence of pain and jaundice, but that it illustrates well the prolonged course typical of this tumor.

CASE REPORT

A 49 year old Italian woodworker was seen for the first time in January, 1952, with a complaint of chills and fever of one year's duration.

In December, 1950, he had had a short shaking chill without other symptoms. Three days later a similar chill occurred. Following this he had recurrent shaking chills and fever occurring approximately once every two or three weeks, easy fatigability and occasional night sweats for a period of six months. These symptoms then stopped spontaneously for several months, only to recur with increased frequency. He was then having chills one to two times weekly, followed by fever for eight to 10 hours. The chill usually started late in the afternoon, and by the next morning the patient was afebrile and would go to work.

In November, 1951, he entered another hospital where almost daily chills and fever spiking to 103° to 104° F. were observed. A diagnostic study, including gall-bladder series, gastrointestinal series, intravenous pyelogram and repeated cultures of blood, stool and urine, failed to reveal any abnormality. The sedimentation rate was elevated and the leukocyte count was 11,000. A trial course of chemotherapy including Gantrisin, penicillin and streptomycin was begun, and within three days the patient became afebrile and remained so throughout the rest of his stay. He returned home and shortly thereafter stopped medication. Within three days he had a return of fever without chills or night sweats.

Physical Examination: Temperature was 38.7 C.; pulse, 88; respirations, 20; blood pressure, 138/80 mm. of Hg.

The patient was a well developed male in no acute distress, appearing neither acutely nor chronically ill. Positive physical findings were limited to a soft apical systolic murmur without cardiac enlargement, a firm sharp nontender liver edge extending 5 cm. below the right costal margin, and an enlarged spleen felt only in the right decubitus position.

Laboratory Data: Urine: negative except for transient 2 plus albumin. Blood: hemoglobin, 12.7 gm.; erythrocytes, 4,200,000; hematocrit, 37 per cent; leukocytes, 5,300, with 36 per cent lymphocytes, 17 per cent monocytes, 2 per cent eosinophils,

24 per cent polymorphonuclear forms, and 21 per cent band forms. Blood urea nitrogen, 11 mg. per cent; albumin/globulin, 4.3/2.3. Stool: four specimens negative for blood (guaiac test).

Blood chemistry: bilirubin, 1.4 (normal 0.7); alkaline phosphatase, 12.0 units (normal 4.0); thymol turbidity, 3 units (normal 5); cephalin flocculation, 9 units (normal 6). Duodenal drainage: culture of *Escherichia coli*, cytology of cells Papanicolaou Class I—no evidence of malignancy. Gall-bladder series: nonfunctioning. Gastrointestinal series revealed a diverticulum of the second portion of the duodenum.

Blood cultures, negative on 12 occasions. Stool cultures, negative for *Salmonella* and *Shigella*, and negative for ova and parasites. Blood and bone marrow smears, negative for malarial parasites. Widal and *Brucella* agglutinations, negative.

Blood Mazzini, negative. Fecal urobilinogen, 360 units/100 gm. (normal, 40–280). Barium enema, abdominal x-ray, chest x-ray and intravenous pyelogram, all normal. Electrocardiogram, normal. Proctoscopy, normal.

Course: During the first two weeks of hospitalization the patient had six episodes of afternoon shaking chills followed by temperature elevation up to 39.5° C., but no other symptoms. Because of the suspicion of malaria, he was given a trial of quinine and pentaquin therapy, without effect. On one occasion the leukocyte count rose to 16,000, with a shift to the left during a febrile episode.

The bilirubin varied between 0.5 and 1.6. The alkaline phosphatase decreased from 12.5 to a normal level of 3.5. The remainder of the blood chemistry examinations remained as on admission. It seemed most likely that the patient had chronic gall-bladder disease with resultant cholecystitis, possible common duct stone and recurrent cholangitis, giving the clinical picture of Charcot's intermittent fever.

On February 16, 1952, an exploratory laparotomy was performed. The liver and spleen were found to be of normal size. The gall-bladder was thickened but not enlarged. The common bile duct was approximately twice normal size. A cholangiogram revealed good filling of the biliary tree with reflux into the pancreatic duct. No dye appeared in the duodenum. An exploration of the common duct failed to reveal stone or tumor. As it was not possible to pass a probe through the ampulla of Vater, a duodenotomy was performed. Palpation and inspection of the ampulla revealed no further abnormality. Dilatation was accomplished without difficulty, and a T-tube was inserted into the common duct. The operative diagnosis was ampullary stenosis.

Postoperatively the patient did well. During the next four months he remained afebrile, with the T-tube in place. The alkaline phosphatase and cephalin flocculation tests remained abnormal. In November, nine months after operation and five months after removal of the T-tube, he had his first recurrence of shaking chill and fever. For the first time he also had mild aching epigastric pain. Accompanying this was a leukocytosis and a rise in the serum amylase. There was no bile in the urine. Physical examination revealed right upper quadrant tenderness and a palpable but nontender liver edge, as before. He was readmitted to the hospital.

Fever and chills again subsided rapidly on antibiotic therapy. Acute pancreatitis was suspected because of the elevated serum amylase. He did well and was discharged afebrile after five days, to continue antibiotic therapy. Two days after antibiotics were stopped the symptoms recurred. Again antibiotics rapidly controlled the fever; the serum amylase decreased from 366 to 45, and the bilirubin from 1.5 to 0.5. At this point it was the opinion of both medical and surgical services that a sphincterotomy was indicated, to provide more satisfactory biliary drainage and to prevent the recurrent episodes of pancreatitis and cholangitis.

On January 9, 1953, a second laparotomy was performed. An enlarged nodular pancreas was found which appeared to be the site of recent inflammation. The pressure in the bile duct was 180 mm. of bile. Through a duodenotomy the ampulla of

Vater appeared prominent and about the size of the end of the small finger. On opening the ampulla small papillomatous tags were noted, the largest being 5 mm. in length and projecting into the lumen. These lesions were biopsied and a wedge was removed from the ampulla for pathologic examination. The common channel was obliterated, the pancreatic duct and common bile duct being re-implanted separately in the duodenum. A cholecystectomy was then performed.

Pathologic examination of the biopsy specimens from both the papillomatous area and the wedge of ampulla revealed carcinoma of the ampulla of Vater. In the ampulla the tumor cells were seen to undermine the mucosa and spread into the smooth muscle.

The patient's postoperative course was uneventful. Because of the finding of a malignant tumor, a third operation was performed on February 6, 1953. This procedure consisted of a subtotal pancreatectomy, choledochojejunostomy, duodenectomy, partial transverse colectomy, subtotal gastrectomy and a gastrojejunostomy. Serial sectioning of the region of the re-implanted bile and pancreatic ducts and regional nodes failed to reveal any remaining malignant cells.

His postoperative course was complicated by both a colo-cutaneous fistula and a pelvic abscess. The former was almost closed at the time of discharge, and the latter was well controlled and subsided on chemotherapy. A gastrointestinal series demonstrated a well functioning gastric stoma. All liver function studies were within normal limits.

COMMENT

This case illustrates well that, although the most common cause of Charcot's fever is a common duct stone, intermittent biliary obstruction from any cause may reproduce the clinical picture.

There is little doubt that the intermittent fevers experienced by this patient for two years were the result of intermittent biliary obstruction with secondary infection of the biliary tract. The long symptom-free periods which he experienced while on adequate antibiotic therapy or external biliary drainage indicate well their efficacy in controlling the infection, but also their failure to alter the underlying cause.

One might easily have attributed this patient's symptoms to a biliary dyskinesia or dyssynergia. That this in itself is rarely if ever a primary cause of biliary symptoms is stressed by Rothman,⁴ who stated that "... we have been unable, in a single instance, to agree upon a diagnosis of biliary dyssynergia to account for biliary tract symptoms in patients who have not been operated upon or in those without anatomic defect or disease of the biliary tract."

Many authors have noted that, for its size, there is probably no other tumor that causes such widespread symptoms as carcinoma of the ampulla of Vater. In spite of this it is seldom suspected as a cause of biliary obstruction. This has been emphasized by Sharpe and Comfort,⁵ who show that in their 40 cases of this tumor it was clinically suspected only once. In their report, weight loss, pain, chills and fever, diarrhea and a palpable gall-bladder were each found in more than 50 per cent of their cases. It is interesting to note that in this case clinical jaundice was never present, and abdominal pain was minimal and appeared very late in the patient's course.

Wide surgical excision offers cure or prolonged palliation. Pancreaticoduodenal resection is the current procedure of choice. Cattell and Pyrtle,⁶ in reporting their results in a series of ampullary carcinomas, show a three year survival of 50 per cent and a five year survival of 25 per cent. They and others

stress the curability as compared to other tumors in this region, which are usually more malignant.

It is fortunate not only that carcinoma of the ampulla grows in such a strategic position that it causes early signs and symptoms of biliary obstruction, but also that it invades the surrounding tissue slowly and metastasizes late and often only locally.⁷ Anderson⁷ states that tumors of the ampulla may be papillary or ulcerative, composed of glandlike or ductile spaces lined by cuboidal or columnar epithelium, often with papillary irregularities. Mucus production or solid masses of cells may occur. The small tumor found in this case, with invasion of the smooth muscle but without demonstrable metastases, is therefore more typical than exceptional. It would seem to be unique, however, because of the very long period of illness, and the apparent complete removal of the tumor by biopsy two years after the onset of symptoms.

SUMMARY

A case of carcinoma of the ampulla of Vater is presented in which the major manifestation was a Charcot-type intermittent fever of two years' duration. Clinical jaundice never appeared, and abdominal pain was of mild degree and appeared late in the course. It should be recognized that in these tumors the onset of symptoms is early and the prognosis is favorable with adequate surgical excision, because invasion is local and metastases occur late. Intermittent biliary obstruction rarely occurs in the absence of anatomic defect or disease.

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MEDIASTINAL TUMOR SIMULATED BY AZYGOS PHLEBECTASIA *

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THE normal azygos vein produces a recognizable radiographic shadow in a variable number of posterior-anterior chest roentgenograms.¹ Less frequently

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the x-ray image of a dilated azygos vein has been mistaken for a mediastinal tumor.^{2, 3, 4, 5} In fact, on occasion, patients with subsequently proved intrathoracic azygos phlebectasia or other vascular abnormalities have received the "therapeutic trial" of irradiation therapy^{2, 5, 6, 7} so recently deprecated by Peabody.⁸

This report is concerned with two illustrative case histories, the basic etiology of azygos phlebectasia, and the specific methods of differentiating this entity from a true mediastinal tumor.

CASE REPORTS

Case 1. A 39 year old white female was transferred to Walter Reed Army Hospital with the diagnosis of involutional melancholia, bilateral varicosities of the lower extremities, and a right inguinal hernia. She refused psychiatric care for the first diagnosis, but requested appropriate treatment for the varicosities and hernia. Generalized varicosities of the left lower extremity were first noted following postpartum thrombophlebitis at the age of 30. She was treated at that time with sodium morrhuate injections. In 1944 a bilateral high saphenous ligation was performed, and

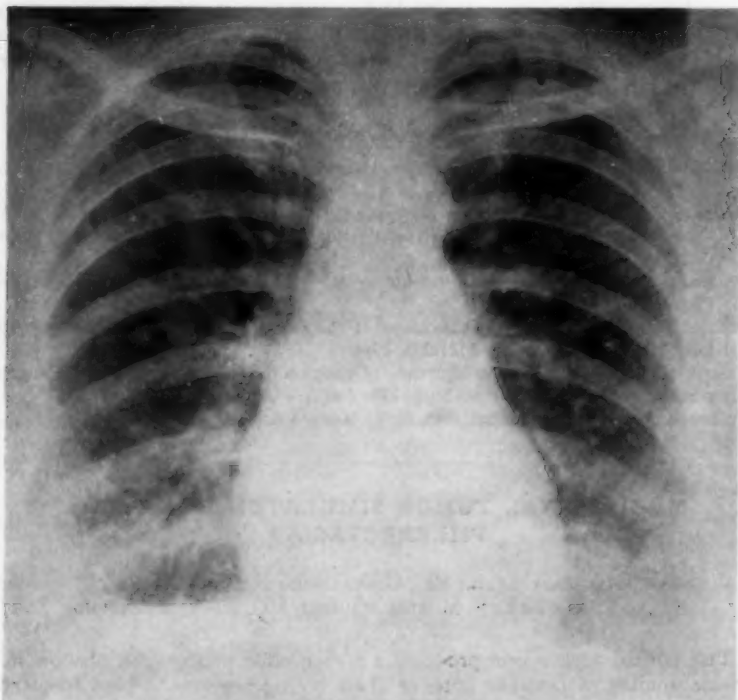


FIG. 1. *Case 1.* Posterior-anterior view of the chest showing the rounded shadows in the right mediastinum.

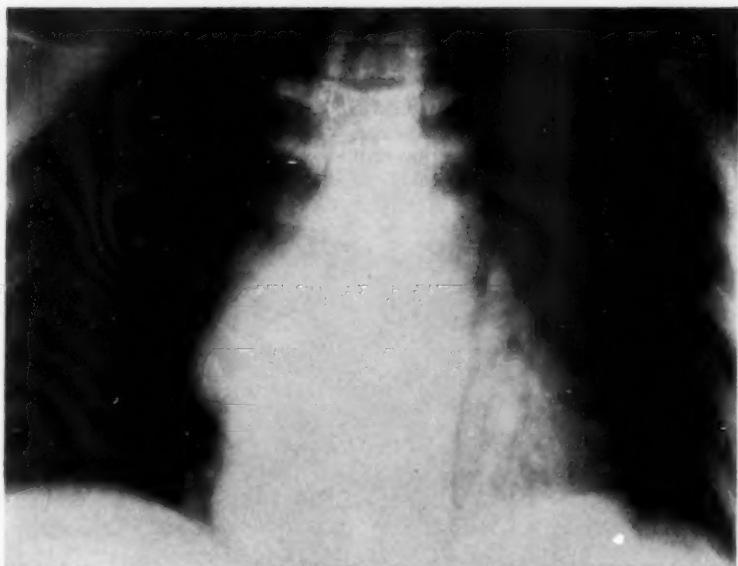


FIG. 2. Case 1. Chest tomogram illustrating clearly the multilobular densities of the right mediastinal area.

in 1948 the right lesser saphenous vein was ligated. In 1950 and 1951 the affected veins in the lower extremities were treated by multiple procedures including stripping, spot ligation and injection with sclerosing agents. In September, 1950, following minor trauma to the right inguinal region, the patient developed an inguinal hernia.

Past History: At 12 years of age and again at the age of 18 she had had single episodes of painless hematemesis, but did not require blood transfusion.

Physical Examination: Significant abnormalities were enlargement of the liver 5 cm. below the right costal margin, and a firm, nontender enlargement of the spleen 8 cm. below the left costal margin. Marked bilateral varicosities of the greater and lesser saphenous veins, with multiple injection and ligation scars, epidermal atrophy, pigmentation and slight pitting edema of the lower extremities, were present. A small reducible right inguinal hernia was also noted. There was no evidence of ascites, hemorrhoids or the development of collateral circulation.

Laboratory Data: Complete laboratory studies were performed and the only abnormalities found were a persistent granulocytic leukopenia of 2,450 to 4,000, 3 plus cephalin flocculation test, and a zinc sulfate turbidity test of 5 units (normal in this laboratory, 0 to 3.5 units).

Special Examinations: Electrocardiograms on two occasions revealed nonspecific T wave abnormalities in precordial leads V_2 through V_6 . Sternal aspiration revealed the bone marrow to be normal in all respects. The intradermal tuberculin test was negative in both first and second strengths. A liver biopsy obtained at the time of the operation was reported as showing minimal portal fibrosis with bile duct proliferation. Angiocardiography was not performed, because the patient reacted to a test dose of the contrast medium with angioneurotic edema and laryngospasm. Esophagoscopy was not performed.

Radiologic Data: Routine posterior-anterior view of the chest revealed rounded densities of the right mediastinum (figure 1). Survey film of the abdomen confirmed the hepatosplenomegaly, and a skeletal survey showed no osseous lesions. Cardiac fluoroscopy was within normal limits. The chest tomogram showed that the mediastinal masses were more extensive than had been suspected (figure 2), and kymography showed them as being nonpulsatile.

Hospital Course: Upon completion of the necessary investigative procedures it was evident that the nature of the mediastinal masses remained to be determined. On

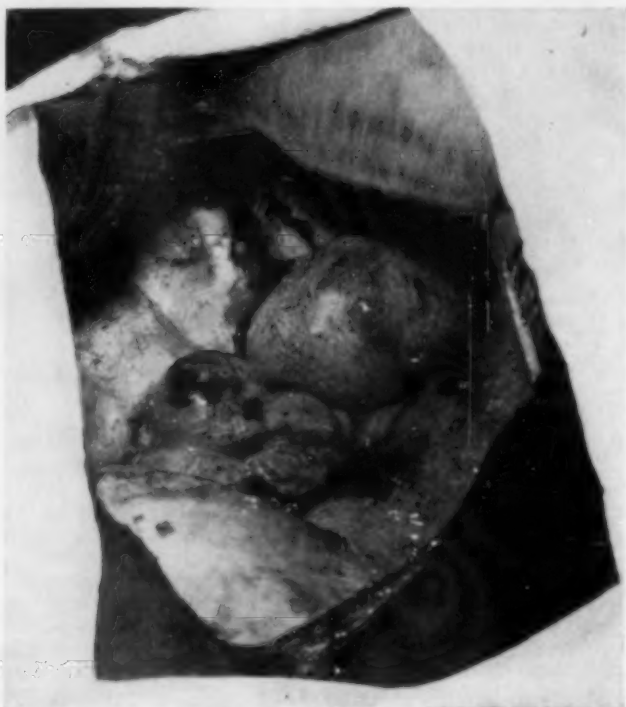


FIG. 3. Case 1. Direct view of the right thoracic cavity at operation. The right hemidiaphragm is in the left lower corner of the draped area. The remarkably dilated and tortuous azygos vein is noted in the center.

the thirty-fifth hospital day an exploratory thoracotomy was performed. When the right lung was retracted anteriorly a distinct enlargement of the azygos system of veins was seen to extend from the diaphragm to the apex of the lung (figure 3). The superior vena cava was also remarkably dilated at its junction with the azygos vein. Palpation of the inferior vena cava as it passed through the diaphragm suggested that it carried very little blood and was smaller than would normally be expected. There was no evident obstruction to explain the azygos dilatation. Since it was apparent that these veins were functioning collateral channels, the chest was

closed. The patient had an uneventful postoperative recovery, but no follow-up studies have been possible.

Case 2. A 20 year old Negro male was admitted to Walter Reed Army Hospital with a history of never having been able to engage in strenuous physical activity because of dyspnea and diminished tolerance to exercise. At 18 years of age he had

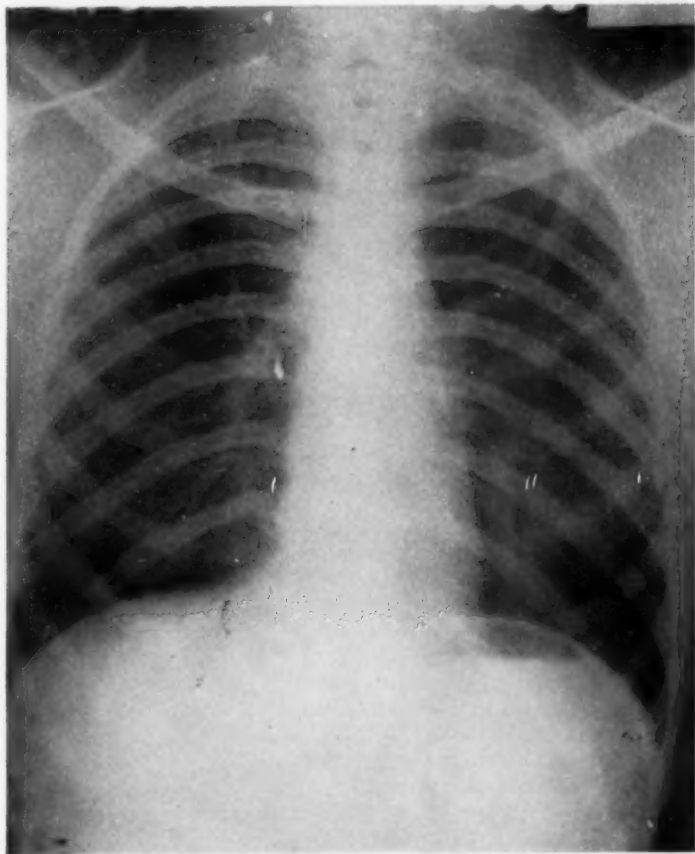


FIG. 4. *Case 2.* Posterior-anterior view of the chest showing the rounded shadow in the right superior mediastinum.

first noted the additional symptom of facial edema, which appeared only after a night of rest and disappeared during the day. After military induction in April, 1952, he was able to complete Army basic training with difficulty. When the patient reported to a dispensary because of an acneform rash on his face and neck, the examining physician observed dilated veins of the anterior chest region and recommended hospital evaluation. Physical examination revealed bilateral facial edema, nonpulsating

distention of the external jugular veins bilaterally, and prominent venous distention of all veins of both upper extremities. Dilated tortuous veins were present in the skin of the epigastric and anterior thoracic regions, and the blood flow of these vessels was demonstrated to be cephalocaudad in direction. There was a moderately severe acneform skin rash on the face and neck. Firm, nontender discrete lymph nodes were palpable in the submandibular, anterior cervical and inguinal areas. There were no other significant abnormal physical findings.

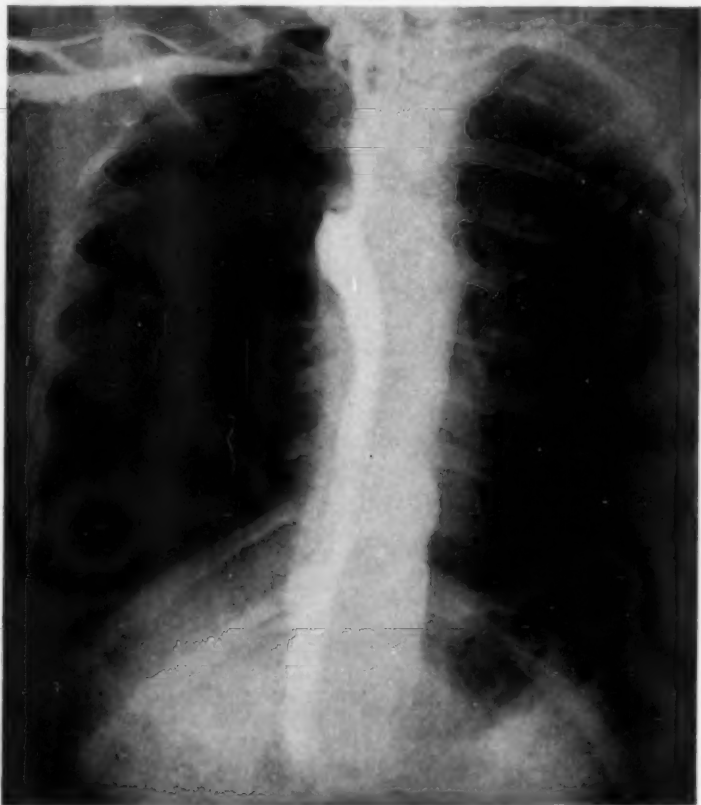


FIG. 5. Case 2. Angiocardiogram demonstrating the dilated azygos vein and failure of the contrast substance to enter the heart due to obstruction of the superior vena cava.

Laboratory Data: Complete blood count, urinalysis and serologic test for syphilis were within normal limits. Corrected sedimentation rate was 29 mm., and a posterior-anterior chest x-ray (figure 4) demonstrated a widening of the right superior mediastinum which was considered to be either a tumor mass or a dilated azygos vein.

Special Studies: Venous pressure in the upper extremities was 300 mm. of water and in the saphenous vein 120 mm. of water. Bronchography revealed an anomalous

right upper lobe bronchus, but bronchoscopy was negative. Fifty milliliters of a 70 per cent Diodrast solution was injected into the right antecubital vein, resulting in the demonstration (figure 5) of a dilated azygos vein and obstruction of the superior vena cava. Additional contrast medium introduced via the saphenous vein revealed no abnormality of the inferior vena cava, heart or aorta.

Hospital Course: A thoracotomy was performed to determine the nature of the obstruction of the superior vena cava. The latter was found to be a hard fibrous cord extending from the heart to the second portion of the right subclavian vein subjacent to the anomalous right upper lobe bronchus. An enlarged tortuous azygos vein, with several other dilated venous channels, was noted. Definitive surgery was not indicated, and the chest was closed. The patient's recovery was uneventful and he was subsequently discharged from the military service.

DISCUSSION

Pathologic dilatation of the azygos vein results when obstruction of one of the greater venous circuits occurs sufficient to warrant utilization of this route of collateral circulation. The detailed anatomy of the collateral circulation following great vein occlusion has been adequately studied and discussed by Carlson⁹ and others.^{2,3,6} Azygos phlebectasia has been reported in association with obstruction of the superior vena cava, occlusion of the inferior vena cava, portal hypertension and congestive heart failure.¹ Unfortunately, clear differentiation could not be made between portal hypertension and obstruction of the inferior vena cava as the cause for the extremely dilated azygos vein (figure 3) found in case 1. In case 2 the cause was clearly the occluded superior vena cava, which was probably due to an old thrombosis, and possibly related to the close proximity of the anomalous bronchus.

It should be emphasized that the presence of a shadow of the azygos vein on a roentgenogram, as such, does not indicate the presence of a pathologic process such as great vein occlusion. However, when this shadow is of such magnitude as to simulate a tumor, the possibility of these factors must be considered. Such consideration should logically lead to the application of the various procedures of value in the detection of intrathoracic vascular abnormalities. These include tomography, special radiographic views combined with certain respiratory maneuvers, angiocardiology and, if necessary, exploratory thoracotomy.

Chest tomography will frequently disclose the shadow of the normal azygos vein,¹ and certainly that of a dilated vein. In some instances this procedure will have no diagnostic value, as illustrated by our experience with case 1, in which the distinct lobular shadows (figure 2) would have been compatible with lymphoma.

Stauffer¹ has emphasized the value of obtaining either posterior-anterior or right anterior oblique films before and during the performance of certain respiratory maneuvers. The radiographic shadow of an azygos vein will increase in size during an attempt at forced inspiration against a closed glottis—Müller's maneuver—and will decrease during the execution of the Valsalva maneuver. Obviously, these alternations are produced by the resultant changes in intrathoracic pressure.

Undoubtedly, the most reliable means of determining whether a particular radiographic shadow is of vascular origin is angiocardiology as originally

described by Robb¹⁰ or as modified by Jacobs et al.¹¹ The angiocardigram of case 2 is illustrated in figure 5. The sensitivity to the contrast medium manifested by case 1 illustrates one of the serious shortcomings of this procedure. Certainly we are in agreement with Abbott et al.⁷ that this procedure is of great value in the study of radiographic shadows of the right superior mediastinum.

Finally, thoracotomy must be performed occasionally (as in case 1) to explain the roentgen appearance of the chest, or to determine the nature of the venous obstruction (as in case 2). Should the lesion prove not to be vascular, the opportunity is thereby afforded for the biopsy specimen and precise histologic diagnosis upon which appropriate therapy should rely.

It is apparent that early application of these procedures to patients presenting radiographic evidence of mediastinal tumor will result in increased clarity of diagnosis, adequacy of therapy and validity of prognosis.

SUMMARY

1. Two case histories are reported illustrating the fact that radiographic evidence of a mediastinal tumor can be simulated by azygos phlebectasia.

2. Azygos phlebectasia has occurred because of obstruction of the superior vena cava, occlusion of the inferior vena cava, portal hypertension or congestive heart failure.

3. The detection of this entity by the utilization of chest tomography, special radiographic views in combination with certain respiratory maneuvers, angiocardiology and thoracotomy is discussed.

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EDITORIAL

NALORPHINE HYDROCHLORIDE, N.N.R. ("NALLINE HYDROCHLORIDE")

ALTHOUGH morphine has been one of the most important drugs in the physician's armamentarium for many years, its serious disadvantages have always been recognized. Along with the dangers inherent in overdosage of the drug, serious side effects have limited its usefulness—depression of the respiration, slowing and weakness of the pulse, constipation, nausea and vomiting, excitation in some individuals and the ever present danger of addiction.

Because of these disadvantages and the virtual indispensability of morphine for the relief of severe pain, many attempts have been made to find substitutes possessing the analgesic properties of morphine but devoid of its serious side effects. The complexity of the morphine molecule has given chemists an opportunity to prepare many synthetic derivatives, and chemical alteration of the natural product has resulted in compounds having increased analgesic activity (heroine, Dilaudid), decreased analgesic activity (codeine, Dionin) or entirely different properties (apomorphine). Other useful drugs (methadone, Demerol, Dromoran), while not morphine derivatives, bear some chemical relationship to morphine and exhibit some of its toxic and addictive properties.

In 1941 McCawley and co-workers¹ reported on the synthesis of a compound differing from morphine only by the substitution of an allyl for a methyl group on the nitrogen atom of the heterocyclic ring. This compound, N-allylnormorphine (Nalorphine Hydrochloride, N.N.R., "Nalline Hydrochloride") was studied pharmacologically by Unna² and Hart and McCawley³ who found it to be an effective antagonist to the analgesic, sedative and respiratory depressant actions of morphine. Other workers have studied the drug in greater detail and found it to be equally effective in combating the effects of methadone, Dilaudid, Dromoran, Pantopon and Demerol.^{4a-1}

¹ McCawley, E. L., Hart, E. R., and Marsh, D. F.: Preparation of N-allylnormorphine, *J. Am. Chem. Soc.* **63**: 314 (Jan.) 1941.

² Unna, K.: Antagonistic effect of N-allylnormorphine upon morphine, *J. Pharmacol. and Exper. Therap.* **79**: 27-31 (Sept.) 1943.

³ Hart, E. R., and McCawley, E. L.: Pharmacology of N-allylnormorphine as compared to morphine, *ibid.* **82**: 339-348 (Dec.) 1944.

^{4a} Smith, C. C., Lehman, E. G., and Gilfillan, J. L.: Antagonistic action of N-allylnormorphine upon the analgetic and toxic effects of morphine, methadone derivatives and Isonipeaine, *Fed. Proc.* **10**: 335-336 (March) 1951.

^{4b} Huggins, R. A., Glass, W. G., and Brown, A. R.: Protective action of N-allylnormorphine against respiratory depression produced by some compounds related to morphine, *Proc. Soc. Exper. Biol. and Med.* **75**: 540-541 (Nov.) 1950.

^{4c} Eckenhoff, J. E., Elder, J. D., and King, B. D.: The effect of N-allylnormorphine in treatment of opiate overdose, *Am. J. M. Sc.* **222**: 115 (July) 1951.

^{4d} Eckenhoff, J. E., Elder, J. D., and King, B. D.: N-allylnormorphine in the treatment of morphine or Demerol narcosis, *Am. J. M. Sc.* **223**: 191-197 (Feb.) 1952.

All investigations to date indicate that nalorphine is a specific narcotic antagonist. It is not active against the depression produced by cyclopropane, ether, nitrous oxide, barbiturates or other depressant drugs of non-narcotic character. It promptly reverses the respiratory depression and increases both the minute volume and rate of respiration in patients depressed by large doses of narcotics. It also prevents the occurrence of respiratory depression when administered prior to (about 30 minutes) a large therapeutic dose of morphine. The drug may also reverse the fall in blood pressure, decrease in pulse pressure, cardiac arrhythmia and loss of the superficial and deep reflexes produced by narcotic drugs. It alters the electroencephalographic pattern from that of deep sleep to that of the waking state in patients poisoned with morphine and its derivatives.

While it is frequently desirable to administer narcotics to relieve pain during labor, doctors are ever conscious of the possibility of such drugs producing profound respiratory depression in the fetus. The depression caused by barbiturates, scopolamine, and narcotic analgesics during the first stage of labor and frequently intensified by inhalation anesthetics during labor increases the risk of severe respiratory depression in the mother and the newborn. With these facts in mind, Eckenhoff and associates^{40, 5} studied the use of intravenous nalorphine in combating neonatal narcosis produced by parturient sedation. In extensive studies involving more than a thousand deliveries, they found that infants born to mothers receiving nalorphine and narcotics, without general anesthesia, showed a significant reduction in the need for resuscitation and in the time required to gasp and breathe. The efficacy of nalorphine was reduced when narcotized mothers received nitrous oxide anesthesia, but there still was a significant shortening of time to gasp and breathe, and decreasing need of resuscitation. The narcotic antagonistic effects of nalorphine were not apparent in infants born to opiate treated mothers who had also been given ether anesthesia. These workers also used nalorphine successfully in the treatment of neonatal apnea due to maternal narcosis by injecting the drug directly into the umbilical cord vein of apneic infants who had received oxygen and artificial respiration because they failed to breathe spontaneously after delivery. Further in-

⁴⁰Eckenhoff, J. E., Hoffman, G. L., and Dripps, R. D.: N-allylnormorphine: an antagonist to the opiates, *Anesthesiology* **13**: 242-251 (May) 1952.

⁴¹Chase, H. F., Boyd, R. S., and Andrews, P. M.: N-allylnormorphine in treatment of dihydromorphinone and methorphan overdosage: report of a case, *J. A. M. A.* **150**: 1103-1104 (Nov. 15) 1952.

⁴²Bornstein, M., Yorburg, L., and Johnston, B.: N-allylnormorphine in treatment of methorphan (Dromoran) hydrobromide poisoning, *J. A. M. A.* **151**: 908-910 (March 14) 1953.

⁴³Domino, E. F., Pelikan, E. W., and Traut, E. F.: Nalorphine (Nalline) antagonism to racemorphan (Dromoran) intoxication, *J. A. M. A.* **153**: 26-27 (Sept. 5) 1953.

⁴⁴Wikler, A.: Effects of large doses of N-allylnormorphine on man, *Fed. Proc.* **10**: 345 (March) 1951.

⁵Eckenhoff, J. E., Hoffman, G. L., Jr., and Funderburg, L. W.: N-allylnormorphine: an antagonist to neonatal narcosis produced by parturient sedation. Presented before A. M. A. Meeting, Chicago, June, 1952.

vestigation of this use is required, and it must be remembered that nalorphine is ineffective in the treatment of asphyxia of non-narcotic origin in the newborn.

In patients severely depressed and in deep coma as a result of narcotic poisoning, nalorphine is only partially effective in lightening the depth of the coma. It is not as effective as it is in relieving respiratory depression. Fraser and co-workers⁶ successfully treated two patients who were severely depressed and in deep coma as a result of methadone poisoning. The respiratory depression was relieved promptly and they regained consciousness within a short time after the administration of nalorphine.

Nalorphine has also been used to obtain partial relief of respiratory depression resulting from a narcotic plus a barbiturate. However, nalorphine does not relieve the depressant action of barbiturates, so the degree of improvement has varied with the relative depressant effect of the narcotic. In inducing inhalation anesthesia, where respiratory depression has resulted from preanesthetic medication with opiates, nalorphine has been employed to relieve this and thus facilitate induction with an inhalation anesthetic.⁷

It has been reported that nalorphine will cause symptoms of withdrawal within 15 minutes when given to narcotic addicts and is therefore a valuable agent for the rapid diagnosis of narcotic addiction.^{8,9,10} However, there is danger involved in this procedure, since the patient may experience violent withdrawal symptoms and a fatality might result. Signs of withdrawal may also occur in individuals who have received several doses of a narcotic for therapeutic purposes. The data available at the present time do not justify recommending nalorphine as a diagnostic in narcotic addiction except by those experienced in dealing with addicts and when doctors and patients are fully aware of risks involved.

Nalorphine does not produce serious toxic effects unless very large doses are given. The lethal dose has not been established in man, but as much as 75 mg. has been given to non-tolerant former morphine addicts without causing dangerous symptoms.¹⁰ However, it is suggested that no more than 40 mg. of nalorphine be administered in a single dose to adults. High dosage is usually accompanied by dysphoria, miosis, pseudoptosis, lethargy, mild drowsiness and sweating. Occasionally nausea, heaviness in the limbs, hot and cold flashes, pallor and postural hypotension are observed. It has

⁶ Fraser, H. F., Wikler, A., Eisenman, A. J., and Isbell, H.: Use of N-allylnormorphine in the treatment of methadone poisoning in man: report of two cases, *J. A. M. A.* **148**: 1205-1207 (April 5) 1952.

⁷ Adriani, J.: Combatting narcotic-induced respiratory depression in surgery, *Merck Report* **62**: 27-29 (April) 1953.

⁸ Isbell, H., and Committee on Drug Addiction and Narcotics of the National Research Council: Report to the Council. "What to do with a drug addict," *J. A. M. A.* **149**: 1220-1223 (July 26) 1952.

⁹ Isbell, H.: Nalline, a specific narcotic antagonist, *Merck Report* **62**: 23-26 (April) 1953.

¹⁰ Wikler, A., Fraser, H. F., and Isbell, H.: Effects of single doses and precipitation of acute "abstinence syndromes" during addiction to morphine, methadone or heroin in man (post addicts), *J. Pharmacol. and Exper. Therap.* **109**: 8-20 (Sept.) 1953.

been observed that nalorphine acts synergistically when given to patients after a dose of morphine which does not cause rather marked depression.^{9, 10} When, however, definite depression has been caused by a narcotic analgesic, nalorphine causes a spectacular increase in respiratory rate and minute volume and elevation of blood pressure, if it has been depressed. Improvement in the patient is generally dramatic. A critical situation may be reversed, with cyanosis disappearing and a deeply comatose patient becoming arousable.

Nalorphine is inactive orally, but acts within seconds when given intravenously and within minutes by subcutaneous injection. In cases of severe narcotic depression, readministration of nalorphine may be necessary an hour or so after revival.

RAYMOND M. BURGISON

REVIEWS

The Suprarenal Cortex: Proceedings of the Fifth Symposium of the Colston Research Society, Held in the University of Bristol, April 1-4, 1952. Edited by J. M. YOFFEY. 232 pages; 19 × 25.5 cm. Academic Press, Inc., New York. 1953. Price, \$6.80.

This comprehensive list of papers, concerning the physiology of the adrenal cortex, was read at the Fifth Symposium of the Colston Research Society at the University of Bristol during the spring of 1952 and recently published in book form. The titles, 20 in all, range from a discussion of the chemistry of ACTH to the use of adrenal steroids in personality disorders. Virtually all of these papers are short, well written, to the point, and readily understood by the non-specialist in the field. The book is intended primarily for the investigator, but will also appeal to the clinician whose curiosity concerning the adrenal cortex extends beyond what side effects to look for and what dosages to employ. The clinician will be particularly interested in the discussions of the adrenal-genital relationships, the rôle of the adrenal glands in infection and intoxication, change in the gland during shock treatment, steroid hormones in skin grafting, their influence on mineral and salt metabolism and surgery of the gland. The list of authors is a distinguished one and includes many of the most eminent names in adrenal cortex research, both here and abroad. The book lacks an index and each paper carries its own bibliography.

D. C. S.

Therapeutics in Internal Medicine. 2nd Ed. Edited by FRANKLIN A. KYSER, M.D., F.A.C.P. 830 pages; 18.5 × 27 cm. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. 1953. Price, \$15.00.

This practical book has changed publishers for its second edition. The present volume represents a larger and improved version in which many of the unevennesses of the earlier production have been ironed out. Seventeen new contributors have joined the ranks, while a number have stepped aside, leaving a total of 84 authors who comprise, in the editor's words, "a group of outstanding men whose investigations and teaching experience in certain phases of internal medicine qualify them to make authoritative statements."

The text basically is limited to therapeutics; but in certain sections, where they seem necessary for an intelligent approach to treatment, physiological principles, clinical descriptions and classifications, and etiological factors have been briefly reviewed in helpful introductory paragraphs. A total of over 280 sections covers the whole range of internal medicine, and chapters on common neurological and dermatological entities are included.

A deficiency of the first edition which has been repaired in the current text was the absence of a section devoted to symptomatic therapy. This has now been included and covers such symptoms as cough, diarrhea, constipation, insomnia and fatigue. A useful table of antibiotic therapy has been incorporated, though some may well question the wisdom of recommending chloramphenicol as the drug of choice in a number of diseases including pertussis. An appendix of diets and tables usefully rounds off this text.

The text as a whole maintains a high standard. It is written for the most part in a highly practical way, so that the reader will have little difficulty in carrying out the writer's suggestions. Readability is again favored by two-column printing on non-

shiny paper. All in all this text may well be recommended to internists, general practitioners, resident staffs and students as a readable and convenient therapeutic referee.

H. J. L. M.

Stammhirn und innere Erkrankungen; Kasuistik, Statistik und Kritik am Beispiel Stammhirnstecksplinterverletzter (Brainstem and Internal Diseases; Case Reports, Statistics, and Criticism in Relation to Injuries with Fragments Remaining in the Brain Stem). By Dr. HANS-WILFRID WEDLER. Monographien aus dem Gesamtgebiete der Neurologie und Psychiatrie Heft 76. 335 pages; 17.5 × 26 cm.; with 66 illustrations. Springer Verlag, Berlin, Göttingen, Heidelberg. 1953. Price: DM 69.—(\$17.00).

Stimulated by a recent revival of interest in the neurogenic origin of certain medical diseases, and the concept of hypertension, diabetes mellitus, thyrotoxicosis, and peptic ulcer as a diencephalosis (a disease due to a localized lesion in the brain stem), the author reports 2,000 cases of cerebral injuries in German soldiers with 56 detailed case reports of brain stem injuries.

Although these are careful, clinical studies, with up to eight year follow-up observations, no autopsies were done and the lesions were localized only by roentgenographic evidence of the position of the metallic splinter fragment, the position of the wound of entrance, and the neurologic signs of damage to surrounding structures.

After evaluating the results from surgical, neurological, and medical points of view, with detailed studies of many autonomic functions, the author critically reviews the experimental and clinical evidence dealing with the central nervous system localization of diabetes mellitus, essential hypertension, thyrotoxicosis, and peptic ulcer. The conclusions deny any discrete central nervous system localization of autonomic functions or internal diseases.

Although effects on diaphoresis, blood sugar, blood pressure, etc. may be observed, most of these are acute and transient phenomena and occur in all types of brain injuries, not exclusively in those with brain damage. None of the author's 2,000 cases developed essential hypertension, diabetes mellitus, thyrotoxicosis, or peptic ulcer. He concludes that a diffuse central nervous system representation must be postulated for autonomic functions and the above diseases.

The rôle of the central nervous system is visualized as a push upsetting the total equilibrium of the organism. If there is a constitutionally weak autonomic nervous system or peripheral organ system, a disease is produced, the type depending on where the lability exists.

The volume is a negative report but appears authoritative and is an important reference for basic neuropathology.

U. S.

Atomic Medicine. 2nd Ed. Edited by CHARLES F. BEHRENS, M.D., Rear Admiral, MC, U. S. Navy, Staff Medical Officer, Eastern Sea Frontier; formerly Director, Atomic Defense Division, Bureau of Medicine and Surgery, Navy Department; Commanding Officer, Naval Medical Research Institute, National Naval Medical Center, Bethesda, Maryland. 632 pages; 15.5 × 23.5 cm. The Williams and Wilkins Company, Baltimore, Md. 1953. Price, \$11.00.

Atomic Medicine is a book edited from contributions by 20 well-known physicians and other scientists who are versed in some phase of atomic energy. The book covers many closely related subjects with its 22 chapters devoted to facts and figures of an atomic disaster and survival methods; basic physics of radioactivity, including

production, measurement and protection; fundamental aspects of radiobiology; radioactive isotopes as tracers; medical application of radioactive phosphorus and iodine; and basic research problems in atomic medicine.

This second edition has been rather extensively revised and the information on atomic energy, as applied to medicine, is amazingly well presented. Most of the material presented is only fundamental but will be sufficient for those physicians who are interested only in obtaining a well rounded basic knowledge of the subject. Those who are interested in more than this basic information, must search elsewhere.

J. M. D.

Clinical Management of Behavior Disorders in Children. By HARRY BAKWIN, M.D., Professor of Clinical Pediatrics, New York University; and RUTH MORRIS BAKWIN, M.D., Associate Professor of Clinical Pediatrics, New York University. 495 pages; 17.5 x 23 cm. W. B. Saunders Co., Philadelphia. 1953. Price, \$10.00.

This is a textbook written by pediatricians for pediatricians. It covers nearly every conceivable topic in the area of understanding and handling the psychological problems met with in pediatric practice. The subject matter is grouped under 12 chapter headings and covers such topics as: growth and development in its physical, intellectual and emotional aspects, emotional problems of the physically handicapped and the diagnosis and treatment of behavior disorders, including the neuroses and psychoses of childhood.

The authors consistently stress organic methods of therapy along with direct giving of advice and changing the environment when that is deemed detrimental. The book suffers primarily from ignoring almost completely the important contributions in this field made by psychoanalytically oriented child psychiatry.

In any field of medicine when one attempts to study and understand the psychological and emotional aspects of his patients he first finds the subject confused by the conflicting schools of thought. The investigator may choose to support one of these schools but he can hardly be called a scientific investigator unless he is able and willing to examine the contributions of other important points of view in his attempt to be as objective as possible. In this book the authors write as though such factors as unconscious conflicts and defense mechanisms do not exist. Because of this bias an important part of the literature of the past 20 years is not mentioned. In fact the bibliography is too heavily weighted with items prior to 1936. As an example, the chapter on stealing lists six articles in its bibliography, not one of them having been published since 1932.

The authors excel in their description of organic methods of treatment. However, the reader will have to look elsewhere to learn modern methods of handling the emotional problems of children.

H. W. N.

Cardiographic Technique, A Manual for Cardiological Technicians. By S. L. BARRON, Member Royal Institution of Great Britain, and A. SCHOTT, M.D., M.R.C.S. 156 pages; 14 x 22 cm. Grune and Stratton. New York. 1952. Price, \$5.50.

The purpose of this book is to "define the important duties and responsibilities of cardiological technicians" and provide the background knowledge necessary for proper performance of these duties. There is a wide range of well-assembled material accompanied by diagrams and illustrations in places where the discussion is more complex. The emphasis seems to be on photographic rather than on direct-writing equipment. While much of the material is merely repetition of that found in most instruction manuals accompanying the equipment itself, the reader here has

the advantage of having all the material related to the subject compiled in a single volume, complete with index. The chapter on "Biological Aspects" seems especially adapted for the technician's point of view. The closing chapter on special equipment provides a note of stimulation, suggesting that future technicians will be working in a larger and more advanced field.

However, there are certain omissions, noticeable especially to those who have worked in a large general hospital where technicians must often assume greater responsibility and exercise a certain amount of ingenuity. Operating room equipment, oxygen apparatus, etc. frequently pose problems deserving of greater mention than given here. The authors present the reader with only the routine patient on whom an electrocardiogram may be taken, overlooking difficulties encountered with irrational patients, patients who have had amputations, patients in traction, etc. Children, and particularly newborn infants, also present difficulties worthy of some discussion. The suggestions for report forms and their preservation are limited and omit many methods in current use. While this book is not as complete as it might have been, as a whole it should be useful for anyone working in cardiography.

D. M. S.

Pediatrics. 12th Ed. By L. EMMETT HOLT, JR., and RUSTIN MCINTOSH. 1542 pages; 17.5 x 25.5 cm. Appleton-Century-Crofts, Inc., New York. 1953. Price, \$15.00.

To many physicians, the appearance of this twelfth edition brings a feeling that the pediatric textbook situation has finally returned to normal. The book has been most carefully written and edited. It seems to have been written with more than the usual emphasis on selection of only well-established facts and principles. A possible exception to this policy may be the presentation of the full-feeding principle of management of diarrheas, a current enthusiasm of one of the author-editors. The more conventional point of view is also presented in this instance. To some, there may seem to be an inadequate amount of detail, particularly in sections on therapy. Such limitation, while conserving space, has also an advantage in tending to avoid passing fancies which could otherwise cause the book to become out-dated at an early date. The sections are followed by key references which conveniently direct the reader to original sources, many dated as recently as 1953.

G. E. G.

BOOKS RECEIVED

Books received during November are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Dystrophia Musculorum Progressiva: Eine Genetische und Klinische Untersuchung der Muskeldystrophien. By PROF. DR. P. E. BECKER. 311 pages; 25 x 17.5 cm. 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, DM 25.65.

Einführung in die Lehre vom Adaptationssyndrom. By HANS SELYE. 164 pages; 23.5 x 15.5 cm. (paper-bound). 1953. Georg Thieme Verlag, Stuttgart; agents for U. S. A.: Grune & Stratton, Inc., New York. Price, kartoniert DM 16.50.

Expert Committee on Plague: Second Report. World Health Organization Technical Report Series No. 74. 13 pages; 24 x 16 cm. (paper-bound). 1953. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 10 cents.

Medical Treatment of Disease. By HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (Hon.), M.A.C.P., Hon. F.R.C.P. (Can.), D.S.M. (A.M.A.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, etc.; DALE G. FRIEND, A.B., M.S., M.D., F.A.C.P., Colonel, M.C., A.U.S., Southwest Pacific and European Theaters, World War II, etc.; and MAURICE A. SCHNITKER, B.S., M.D., F.A.C.P., Lieut. Colonel, M.C., A.U.S., Medical Consultant, Pacific Theater, World War II, etc. Co-editors: BURGESS GORDON, M.D., President and William J. Mullen Professor of Medicine, Woman's Medical College of Pennsylvania, Philadelphia, Pennsylvania; WILLIAM J. KERR, M.D., Professor of Medicine, University of California, Medical School, etc.; and CYRUS C. STURGIS, M.D., Professor of Medicine, University of Michigan, etc. 985 pages; 22 x 17.5 cm. (loose-leaf). 1953. Oxford University Press, New York. Price, \$25.00.

Natal Day Deaths: The Long Neglected and Unaltered Field of Infant Mortality. By HERMAN N. BUNDESEN, M.D., Sc.D. 44 pages; 21.5 x 14 cm. (paper-bound). 1953.

The Symptoms and Treatment of Acute Poisoning. By G. H. W. LUCAS, Professor of Pharmacology, University of Toronto. 308 pages; 17 x 11.5 cm. 1953. The Macmillan Company, New York. Price, \$4.00.

Wonders of Modern Medicine. By STEVEN M. SPENCER; foreword by GEORGE F. LULL, M.D., Secretary and General Manager, American Medical Association. 276 pages; 23.5 x 15.5 cm. 1953. McGraw-Hill Book Company, Inc., New York. Price, \$4.00.

COLLEGE NEWS NOTES

A.C.P. POSTGRADUATE COURSES

FINAL SCHEDULE—SPRING, 1954

- CLINICAL GASTRO-ENTEROLOGY: Louisiana State University School of Medicine, New Orleans, La.; Gordon McHardy, M.D., F.A.C.P., Director; March 15-20, 1954.
- SELECTED SUBJECTS IN INTERNAL MEDICINE: Columbia University College of Physicians and Surgeons, New York, N. Y.; Franklin M. Hanger, M.D., F.A.C.P., Director; March 22-26, 1954.
- ELECTROCARDIOGRAPHY: Wayne University College of Medicine, Detroit, Mich.; Gordon B. Myers, M.D., F.A.C.P., Director; April 19-24, 1954.
- CLINICAL HEMATOLOGY: Northwestern University, University of Illinois and University of Chicago, Chicago, Ill.; Howard L. Alt, M.D., F.A.C.P., Director; Leon O. Jacobson, M.D., F.A.C.P., and Louis R. Limarzi, M.D., F.A.C.P., Co-directors; April 26-30, 1954.
- INTERNAL MEDICINE: Hospital of the University of Pennsylvania, Philadelphia, Pa.; Calvin F. Kay, M.D., F.A.C.P., and Francis C. Wood, M.D., F.A.C.P., Co-directors; one week, possibly the second week in May, after the meeting of the Association of American Physicians at Atlantic City.
- DISEASES DUE TO ALLERGIC AND IMMUNE MECHANISMS: University of Pittsburgh School of Medicine, Pittsburgh, Pa.; Leo H. Crippe, M.D., F.A.C.P., Director; May 17-21, 1954.
- INTERNAL MEDICINE: University of California Medical School, San Francisco, Calif.; Stacy R. Mettier, M.D., F.A.C.P., Director; June 14-18, 1954, the week immediately preceding the A.M.A. Annual Meeting.
- RADIOISOTOPES: Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., and William G. Myers, M.D., F.A.C.P., Co-directors; June 14-18, 1954.

The Postgraduate Bulletin will be published and sent to all members, and to those on the mailing list, during January.

ELECTION TO MEMBERSHIP IN THE AMERICAN COLLEGE OF PHYSICIANS

At a meeting of the Board of Regents, held in Philadelphia, Nov. 15, 1953, the following candidates were elected to membership in the College (Fellows indicated in FULL CAPITALS; Associates, Lower Case):

Albert Adlin.....	Philadelphia, Pa.
Paul Michael Aggeler.....	San Francisco, Calif.
CLARENCE MENDEL AGRESS.....	Beverly Hills, Calif.
John Warren Albright.....	M.C., U. S. Navy
James Elisha Alexander.....	Memphis, Tenn.
Sydenham Benoni Alexander.....	Chapel Hill, N. C.
Mary Daniel Ames.....	Harrisburg, Pa.
Howard Arne Andersen.....	Rochester, Minn.
Angelo Panageotis Angelides.....	Philadelphia, Pa.
Hugh Alexander Arnold.....	Lethbridge, Alta., Can.
MICHAEL ARONOVITCH.....	Montreal, Que., Can.
Frank Herbert Austin.....	M.C., U. S. Army
John William Avera, Jr.....	Knoxville, Tenn.
Arnold Raymond Axelrod.....	Detroit, Mich.

William Stanley Bagnall.....	M.C., U. S. Army
Charles Arthur Bailey.....	Ridgewood, N. J.
Henry Baker.....	Boston, Mass.
Augustus C. P. Bakos.....	Los Angeles, Calif.
Hyman Bakst.....	New York, N. Y.
Lloyd Thomas Barnes.....	New York, N. Y.
Richard Chester Bates.....	Lansing, Mich.
Charles Thomas Batten.....	Los Angeles, Calif.
William Donald Battle.....	Modesto, Calif.
FRANK LOUIS BAUER.....	M.C., U. S. Army
Edmund George Beacham.....	Baltimore, Md.
John Edmond Bechtold.....	New Orleans, La.
IRVING ADDISON BECK.....	Providence, R. I.
NATHAN BECKENSTEIN.....	Brooklyn, N. Y.
Robert Mettler Becker.....	Madison, Wis.
William Harvey Beinfield.....	New York, N. Y.
James Carroll Bell.....	M.C., U. S. Army
MORRIS BERK.....	Piedmont, Calif. (V.A.)
Theodore Clark Bernstein.....	Levittown, N. Y.
Wilbur Carmen Berry.....	M.C., U. S. Army
David Biber.....	Union, N. J.
HYLAN ARTHUR BICKERMAN.....	New York, N. Y.
ALBERT ALFRED BIEDERMAN.....	M.C., U. S. Army
ROY STINSON BIGHAM, JR.....	Charlotte, N. C.
Harold Bernard Bilsky.....	Cleveland Heights, Ohio
TULLY TALBOT BLALOCK.....	Atlanta, Ga.
WILLIAM BLOOM.....	New York, N. Y.
SAMUEL MITCHELL BLUEFARB.....	Chicago, Ill.
VIRGIL HENRY F. BOECK.....	Buffalo, N. Y.
CHARLES BOLLER.....	Rochester, N. Y.
Robert James Bolt.....	Ann Arbor, Mich.
John Duane Bonzer.....	Eugene, Ore.
CRAIG WARREN BORDEN.....	Minneapolis, Minn.
JOSEPH FRANKLIN BORG.....	St. Paul, Minn.
Frank Roosevelt Boyer.....	Allentown, Pa.
Robert William Boyle.....	Fort Thomas, Ky. (V.A.)
Robert Willard Brand.....	Clifton Springs, N. Y.
Hugh George Brereton.....	Oakland, Calif.
George Bennett Brothers.....	Nashville, Tenn.
JAMES CUSHING BRUDNO.....	Quincy, Mass.
Albert Adam Brust, Jr.....	Atlanta, Ga.
L(ESTER) JAMES BUIS.....	Richmond, Va.
James Willis Burks, Jr.....	New Orleans, La.
Malcolm Bates Burris.....	New Orleans, La.
Belton Allyn Burrows.....	Boston, Mass. (V.A.)
IRVING FREDERICK BURTON.....	Detroit, Mich.
EWALD WILLIAM BUSSE.....	Durham, N. C.
John Michael Butterly.....	Hewlett, L. I., N. Y.
Edmund James Callahan, III.....	Boston, Mass.
Robert Ernest Campbell.....	M.C., U. S. Army
Robert Owen Canada, Jr.....	M.C., U. S. Navy
David Burton Carmichael, Jr.....	M.C., U. S. Navy

Haddon McCutcheon Carryer.....	Rochester, Minn.
Adolph David Casciano.....	Jersey City, N. J.
Leonard Castleman.....	Brooklyn, N. Y.
EDWARD PHILIP CAWLEY.....	Charlottesville, Va.
William Cayce.....	Grand Rapids, Mich.
RICHARD CHARET.....	Brooklyn, N. Y.
Aaron David Chaves.....	Brooklyn, N. Y.
Charles Sidney Christianson.....	M.C., U. S. Army
JOHN MARK CHURCH.....	Fort Worth, Tex.
EDWARD A. CLEVE.....	M.C., U. S. Army
Robert Martin Clyne.....	New York, N. Y.
Emanuel Samuel Cohen.....	Atherton, Calif.
Ira Bernard Cohen.....	New York, N. Y.
JACK DEXTER COHEN.....	Boston, Mass.
ISIDOR COHN.....	Brooklyn, N. Y.
Jacob Colsky.....	Brooklyn, N. Y.
Robert Ireland Cord.....	Santa Barbara, Calif.
Harney May Cordua, Jr.....	San Diego, Calif.
EDGAR FRANCIS COSGROVE.....	Pittsburgh, Pa.
Orrie Alexander Couch, Jr.....	Nashville, Tenn.
William Theron Couter.....	Decatur, Ill.
(CHARLES) ARCHIE CRANDELL.....	Greystone Park, N. J.
George Russell Crisler.....	Winter Park, Fla.
Lester Cain Crismon.....	Aruba, N. W. I.
Archer Phlegar Crosley, Jr.....	Madison, Wis. (V.A.)
Richard Corbin Cullen.....	Denver, Colo.
Alvin Joseph Cummins.....	Drexel Hill, Pa.
Michael Mihaly Dacso.....	New York, N. Y.
Jacob Mayr Danish.....	Philadelphia, Pa.
GUY WILSON DAUGHERTY.....	Rochester, Minn.
John William Davis.....	Painesville, Ohio
Raphael Francis DeHoratius.....	Philadelphia, Pa.
José Angel DeJesus.....	San Juan, P. R.
David Louis Deutsch.....	M.C., U. S. Army
EMMANUEL DEUTSCH.....	Boston, Mass.
CHARLES KENDALL DONEGAN.....	St. Petersburg, Fla.
John Donnelly.....	West Hartford, Conn.
John Bell Downing.....	Summerside, P. E. I., Can.
MORRIS DRESSLER.....	Miami, Fla. (V.A.)
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WOLCOTT BALESTIER DUNHAM.....	Memphis, Tenn. (V.A.)
William Robert Durkee.....	Manhattan, Kans.
HUGH LEO DWYER, JR.....	New Haven, Conn.
JOHN CHARLES EAGAN.....	Los Angeles, Calif.
ROBERT HIGGINS EBERT.....	Chicago, Ill.
Jerome Albert Ecker.....	Cleveland, Ohio
Carl Neil Ekman.....	M.C., U. S. Army
Thomas Albert Elliott.....	Elkhart, Ind.
CHARLES D. ENSELBERG.....	New York, N. Y.
ABRAHAM FALK.....	Minneapolis, Minn. (V.A.)
THOMAS WOHLSEN FARMER.....	Chapel Hill, N. C.
Richard Emerson Felder.....	Atlanta, Ga.

KARL FISCHBACH.....	New York, N. Y.
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Edward David Freis.....	Bethesda, Md. (V.A.)
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Richard LaMarr Fulton.....	Columbus, Ohio
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Morton Galdston.....	New York, N. Y.
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George Arnold Hyman.....	New York, N. Y.
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Sherman Robert Kaplan.....	Miami Beach, Fla.
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Michael Charles Kozonis.....	Pontiac, Mich.
Sheldon Ellman Krasnow.....	Maywood, Ill.
Nathaniel Bertrand Kurnick.....	New Orleans, La.
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Alfred Leeds Lane.....	Corpus Christi, Tex.
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JOHN HUNDALE LAWRENCE.....	San Francisco, Calif.
Louis Allen Lazar.....	Middletown, N. Y.
Samuel Earnshaw Leard.....	Waltham, Mass.
Jorma Michael Leinassar.....	Astoria, Ore.
HENRY MARTYN LEMON.....	Boston, Mass.
HERBERT MELVILLE LEVENSON.....	Framingham, Mass.
Leon Levinson.....	Boston, Mass.
Albert Gamaliel Lewis, Jr.....	Birmingham, Ala.

George Norwood Lewis.....	Gary, Ind.
JACOB LICHSTEIN.....	Los Angeles, Calif.
Milton Morton Lieberthal.....	Bridgeport, Conn.
WILLIAM PIERCE LOGAN.....	Lakeland, Fla.
George Beck Long.....	Portland, Ore.
E(GBERT) HUGH LUCKEY.....	New York, N. Y.
Thomas Joseph Luellen.....	Wichita, Kans.
Allison David MacDonald.....	Montreal, Que., Can.
Stephen Lawrence Magiera.....	Omaha, Nebr.
CONNOLLY JAMES MALLOY.....	Montreal, Que., Can.
EMANUEL EMIL MANDEL.....	Atlanta, Ga. (U.S.P.H.S.)
Bruno Anthony Marangoni.....	New York, N. Y.
Ernesto Juan Marchand.....	San Juan, P. R.
Antonio Vincent Mascatello.....	Brooklyn, N. Y.
Joseph Charles Matchar.....	Baltimore, Md.
Mendel Mazer.....	Springfield, Mass.
Robert Vance McCormick.....	Madison, N. J.
John Bowen McDonald.....	Los Angeles, Calif.
John Francis McDonnell, Jr.....	Kansas City, Mo.
Lee Davidson McLean.....	New Orleans, La.
Joseph Hamilton McNinch.....	M.C., U. S. Army
John Cassius Meadows, Jr.....	Galveston, Tex.
JOHN GILMER MEBANE.....	Rutherfordton, N. C.
Louis Harry Mendelson.....	Springfield, Ohio
KARL AUGUSTUS MENNINGER.....	Topeka, Kans.
Harry N. Metzger.....	Philadelphia, Pa.
Albert J. Miller.....	Chicago, Ill.
Winston Rivard Miller.....	Red Wing, Minn.
LUIGI PIETRO MINETTO.....	Brooklyn, N. Y.
WILLIAM EDWARD MOLLE.....	Los Angeles, Calif.
Maxwell Moody, Jr.....	Tuscaloosa, Ala.
John Walker Morledge.....	Oklahoma City, Okla.
Charles Kasile Morris.....	M.C., U. S. Air Force
Robert Allen Morse.....	San Angelo, Tex.
Milton Mitchell Mosko.....	Chicago, Ill.
Alexander Ado Mueller.....	Los Angeles, Calif.
William Lowe Mundy.....	Kansas City, Mo.
Robert Curtis Murphy.....	Quincy, Ill.
WILLIAM GRAYDON MYERS.....	Columbus, Ohio
Emile Coleridge Nash.....	Nashville, Tenn.
MAURICE NATARO.....	Louisville, Ky. (V.A.)
Donald Charles Nellins.....	Waukegan, Ill.
Fenwick Tattnall Nichols, Jr.....	Savannah, Ga.
Leonard Ohringer.....	Chicago, Ill.
O(SCAR) CHARLES OLSON.....	Spokane, Wash.
JAMES ARCHER ORBISON.....	M.C., U. S. Army
Robert Clayworth Painter.....	Grand Forks, N. D.
Albert Dorian Parets.....	New York, N. Y.
Alvin Edward Parrish.....	Washington, D. C. (V.A.)
Morris Pasternack.....	Memphis, Tenn.
Oglesby Paul.....	Chicago, Ill.

LAWRENCE PERLMAN.....	Chicago, Ill.
John Decius Pinto.....	Fayetteville, N. C. (V.A.)
William Nelson Piper, Jr.....	M.C., U. S. Army
Alfred Plaut.....	Topeka, Kans. (V.A.)
Ralph Carleton Pollock.....	San Bernardino, Calif.
Robert Alexander Polson.....	Winnipeg, Man., Can.
MAX POMERANCE.....	Brooklyn, N. Y.
Elmer Buckingham Pratt.....	Denver, Colo.
George Francis Price.....	Brooklyn, N. Y.
JOHN ALAN PRIOR.....	Columbus, Ohio
Herbert I. Puller.....	Roselle, N. J.
Max Nathaniel Pusin.....	Lyons, N. J. (V.A.)
Jerome Radding.....	Fresno, Calif. (V.A.)
OSCAR BENJAMIN RAGINS.....	Chicago, Ill.
Paul Ravenna.....	Chicago, Ill.
RULON WELLS RAWSON.....	New York, N. Y.
Margaret Ruth Read.....	Cleveland, Ohio
Charles Bramwell Rich.....	Edmonton, Alta., Can.
Glenn Hickam Richmond.....	M.C., U. S. Army
Anthony Joseph Richtsmeier.....	Madison, Wis.
Clarence Loveridge Robbins.....	Tucson, Ariz.
Lloyd Wayne Robinson.....	Denver, Colo.
Samuel Rosenfeld.....	Brooklyn, N. Y.
Jacob Rosenwasser.....	Mishawaka, Ind.
Harold Hyman Rothendler.....	New York, N. Y.
Benjamin Rothfeld.....	Perry Point, Md. (V.A.)
Doris Margaret Rowe.....	Phoenix, Ariz.
Manuel J. Rowen.....	Elizabeth, N. J.
LEO RUBENSTEIN.....	New York, N. Y.
Henry George Sahl.....	Philadelphia, Pa.
Everett Herman Sanneman, Jr.....	Louisville, Ky.
Jack Frederick Schaber.....	Orlando, Fla.
Jerome Arthur Schack.....	New York, N. Y.
Irving William Schiller.....	Boston, Mass.
HENRY LOUIS SCHMIDT, JR.....	New Orleans, La. (V.A.)
Truman Gross Schnabel, Jr.....	Philadelphia, Pa.
HAROLD OTTO SCHNEIDER.....	Salem, Ore.
JOSEPH ATLAS SCHWARTZ.....	San Fernando, Calif. (V.A.)
DAVID WILLIAM SCOTT, JR.....	Fredericksburg, Va.
William Kent Scupham.....	Chicago, Ill.
STEWART PINNELL SEIGLE.....	Hartford, Conn.
Louis Albert Selverstone.....	Boston, Mass.
Charles Sheard, Jr.....	Stamford, Conn.
John Austin Sheedy.....	M.C., U. S. Army
Leland Parmater Shipp.....	Battle Creek, Mich.
NORMAN SHURE.....	Los Angeles, Calif.
Felix Abraham Silverstone.....	Brooklyn, N. Y.
Ray Hamilton Skaggs.....	Houston, Tex.
JOHN CLARK SLAUGHTER, JR.....	Evansville, Ind.
Gadiel Morris Smith.....	Wilkes-Barre, Pa. (V.A.)
Hugh Percival Smith, Jr.....	Greenville, S. C.
John Robert Snavely.....	New Orleans, La.

DONAL ROSS SPARKMAN.....	Seattle, Wash.
ARNOLD STANTON.....	Richmond Hill, N. Y.
Lorel Aaron Stapley, Jr.....	Phoenix, Ariz.
Stanley Stark.....	Brooklyn, N. Y.
William Anthony Steiger, 3rd.....	Philadelphia, Pa.
Joseph Maxwell Stein.....	Camden, N. J.
Harold Glenn Stevens.....	Los Angeles, Calif.
JULIUS EDWARD STOLFI.....	Brooklyn, N. Y.
Chauncey Montague Stone, Jr.....	Miami, Fla. (V.A.)
LEE STOVER.....	Lincoln, Nebr.
WILLIAM DAVID STRAYHORN, JR.....	Nashville, Tenn.
BENJAMIN ANDERSON STRICKLAND, JR.....	M.C., U. S. Air Force
(Marca) Isabel Taliaferro.....	Richmond, Va.
Robert White Talley.....	Little Rock, Ark.
Felix Taubman.....	Brooklyn, N. Y.
Bowen Eacritt Taylor.....	Lincoln, Nebr.
James Alexander Taylor.....	Chapel Hill, N. C.
Joseph Francis Tedesco.....	Castle Point, N. Y. (V.A.)
Arthur Raymond Thomas.....	Philadelphia, Pa.
ALEXANDER IRWIN THOMASHOW.....	Brooklyn, N. Y.
John Long Thompson, Jr.....	Sylacauga, Ala.
T(HOMAS)EWING THOMPSON, JR.....	Pittsburgh, Pa.
Clifford Tillman.....	Natchez, Miss.
Jerome Norman Tober.....	Los Angeles, Calif.
LEANDRO MAUES TOCANTINS.....	Philadelphia, Pa.
Theodore Francis Treuting.....	New Orleans, La.
WILLIAM BOOSE TUCKER.....	Minneapolis, Minn. (V.A.)
MAURICE TULIN.....	New York, N. Y.
I(SAAC) FRANK TULLIS, JR.....	Memphis, Tenn.
JAMES BAKER TWYMAN.....	Charlottesville, Va.
Walter George Unglaub.....	New Orleans, La.
Allison Richard VandenBerg.....	Grand Rapids, Mich.
John Belden Vander.....	Framingham, Mass. (U.S.P.H.S.)
Joseph Roger Van Dyne.....	Forest Hills, N. Y.
Jay R. Venema.....	Grand Rapids, Mich.
Charles Frederic Von Salzen.....	Hartford, Conn.
S(HOLOM) O(MI) WAIFE.....	Indianapolis, Ind.
John Richard Walsh.....	Omaha, Nebr. (V.A.)
ISRAEL WALZER.....	Whipple, Ariz. (V.A.)
CHRISTINE WATERHOUSE.....	Rochester, N. Y.
Neill Kendall Weaver.....	New Orleans, La.
WILLIAM MORROW WEBB.....	M.C., U. S. Army
William H. Wehrmacher.....	Chicago, Ill.
Louis Weisfuse.....	Brooklyn, N. Y.
Jacob Irving Weisman.....	Springfield, Mass.
JONAS WEISSBERG.....	Elizabeth, N. J.
Mark Stiles Wellington.....	Framingham, Mass.
Joseph Edward Wener.....	Montreal, Que., Can.
Charles Arthur Werner.....	New York, N. Y.
William Albert Werner.....	St. Louis, Mo.
William Hudson Westbrook.....	M.C., U. S. Air Force

Robert Elmer Westlake.....	Syracuse, N. Y.
LaVere Gaillard White.....	Staten Island, N. Y. (U.S.P.H.S.)
Leon Holland Whitney.....	Newark, N. J.
Joseph Percivall Whittle.....	Petersburg, Va.
John Winslow.....	Maplewood, N. J.
Sigmund Samuel Winton.....	Chicago, Ill.
Paul Eugene Wisenbaugh.....	Cleveland, Ohio (V.A.)
Edward John Wiss.....	Chicago, Ill.
Edward Trowbridge Wolf.....	Houston, Tex.
Irving Norman Wolfson.....	Worcester, Mass.
Don Ernest Woodard.....	Salem, Ore.
Clarence Crane Woodcock, Jr.....	Nashville, Tenn.
John Allen Worley.....	Alexandria, La.
Joseph Franklin Wright.....	Cincinnati, Ohio
Banff Ogden Young.....	Duncan, Okla.
Ellard Melton Yow.....	Houston, Tex.
Francis Theodore Zinn.....	Cleveland, Ohio (U.S.P.H.S.)

GIFT TO COLLEGE LIBRARY

The College is gratified to acknowledge an autographed copy of "Synovial Fluid Changes in Joint Disease" presented by the authors, Dr. Marian W. Ropes, F.A.C.P., and Dr. Walter Bauer, F.A.C.P., both of Boston. This book has been added to the College Library of Publications by Members.

NEW LIFE MEMBERS

The College is pleased to announce that Dr. P. V. Dilts, F.A.C.P., Springfield, Ill., and Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., President-Elect of the College, have recently become Life Members.

A.C.P. ELECTION OF MEMBERS

The next meetings of the College Committee on Credentials at which action will be taken on proposals for membership will be held Feb. 28 and April 3, 1954. Proposals must be in the Executive Offices 60 days in advance of the meetings of the Committee. It is recommended that all proposals reach the College Governors 90 days in advance to allow them 30 days for local investigation.

A.C.P. ACTIVITIES IN HAWAII

Dr. Nils P. Larsen, F.A.C.P., College Governor for Hawaii, reports that the autumn season was opened with a private dinner at his home on the beach at which all but one member of the College were present. As special guests they had three prospective members who are in the process of qualifying. This dinner meeting was in essence a welcoming dinner to three new members elected at the last Annual Session of the College, and a farewell to two of the Service members who are leaving Hawaii. The program for the coming year was discussed and a report was received from Dr. Morton E. Berk, F.A.C.P., on his trip to the United States and the Annual Session of the College in April, 1953.

On November 12, 1953, the Hawaiian members gave a dinner in honor of Dr. Walter C. Alvarez, F.A.C.P., of Chicago. All of the Hawaiian members except two were present, one being absent because of illness. Two young physicians who are interested in qualifying for membership in the College were present as guests. During the dinner meeting, Dr. Alvarez answered one question from each member. After the dinner, the group retired from the Pacific Club to the Mabel Smythe Auditorium, where Dr. Alvarez addressed the members and friends of the Medical Society on "The Growing Old Process and What Can Be Done About It." The Auditorium was filled to capacity.

On December 8, 1953, Governor Larsen arranged a special meeting of the College members at the Tripler Hospital, the subject of discussion being "Atherosclerosis in Relation to Race, Sex, Diet and Climate."

ACCREDITATION OF HOSPITALS

There are two distinct programs concerned with the accreditation of hospitals: One is conducted by the Joint Commission on Accreditation of Hospitals and refers particularly to general accreditation; the other is the approval of hospitals for intern or residency training. According to the Journal of the American Medical Association, issue of November 7, 1953, the Council on Medical Education and Hospitals of the American Medical Association maintains a field staff that visits those hospitals to be approved for intern or residency training and while doing so, conducts a combined survey of the hospitals from the standpoint of the Joint Commission's program. "It is particularly noted that accreditation by the Joint Commission, while a prerequisite for approval by the Council, does not involve evaluation of the hospital from the standpoint of its educational program. This function is the responsibility of the Council on Medical Education and Hospitals collaborating, in the case of residencies, with the American Boards and the American College of Physicians and the American College of Surgeons."

APPROVED EXAMINING BOARDS

According to the Advisory Board for Medical Specialties, no new examining Boards have been approved since 1951. However, the American Board of Preventive Medicine has been authorized to certify candidates in two fields, Public Health and Aviation Medicine. Training standards in Aviation Medicine are presently being developed, but there has not been any candidate certified in that specialty thus far. There are 19 examining or certifying Boards at present approved by the Council on Medical Education and Hospitals and the Advisory Board for Medical Specialties, 11 of these in the surgical specialties and 6 in the medical specialties, with 2 in the clinical-laboratory field.

COÖPERATIVE RESEARCH FOUNDATION

The Coöperative Research Foundation through its International Science Center, with offices at the California Academy of Sciences, Golden Gate Park, San Francisco, announces a project to establish and operate a number of international science centers, which would serve foreign scientists and engineers visiting the major centers of scientific activity in the United States. The primary object of the program, according to the Foundation, is to stimulate direct working relationships between foreign scientists and their colleagues in the regions to be served by the Centers.

These Centers are to be established with the coöperation of state or local academies of science, and will provide local facilities for scientific visitors from abroad,

especially those whose visits to the United States are sponsored by private interest. The main functions of the Centers will be: (1) to facilitate contact between the visiting scientist and scientific personnel in the regions; (2) to serve as a coordinating agency for international scientific activities in the region; (3) 'to offer such assistance to visiting scientists as other institutions of the region may not be equipped to give.

The Center in San Francisco particularly invites members of the College and other physicians in that area to work with it on developing arrangements for receiving foreign scientists. It states it may have foreign scientists visiting that Center who would be available to speak at meetings held by our San Francisco membership. The Center has access to several traveling funds for foreign scientists and might be able to assist the local membership of the College and of the medical profession in bringing a distinguished physician to that area for an occasional meeting, if desired. It further asks members of the College to submit any suggestions regarding ways in which that Center could make its program more effective through cooperation.

POSTGRADUATE COURSE, FUNDAMENTAL ADVANCES IN INTERNAL MEDICINE

A postgraduate course in Fundamental Advances in Internal Medicine for Internists will be given at the Center for Continuation Study of the University of Minnesota, Feb. 15-17, 1954. This course is under the direct auspices of the University of Minnesota. Dr. Walter L. Palmer, F.A.C.P., Professor of Medicine at the University of Chicago School of Medicine, and Dr. David Shemin, Associate Professor of Biochemistry, Columbia University College of Physicians and Surgeons, New York City, will be guest speakers. Dr. Cecil J. Watson, F.A.C.P., Professor and Head of the Department of Medicine at the University of Minnesota, will direct the course.

NEW EXAMINATIONS ANNOUNCED BY CIVIL SERVICE COMMISSION

The United States Civil Service Commission has announced a new Medical Officer examination for filling the positions of rotating intern, \$2,800 a year, and resident in training in psychiatry and in neurology, \$3,400 to \$4,200 a year, in St. Elizabeths Hospital in Washington, D. C. Appointments are to begin on July 1, 1954.

Appropriate education is required, plus, for the resident positions, successful completion of a full year's internship. No written test is required. Applicants must not have passed their 35th birthday (waived for persons entitled to veteran preference).

Further information is available at many post offices throughout the country and at the U. S. Civil Service Commission, Washington 25, D. C. Applications will be accepted by the Executive Secretary, Board of U. S. Civil Service Examiners, St. Elizabeths Hospital, Washington 20, D. C.

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital by Louis N. Katz, M.D. (Director of the Cardiovascular Department, Medical Research Institute) and associates. The class will meet each Wednesday from 7:00 to 9:00 p.m. for twelve weeks, beginning February 3.

Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Rivian H. Lewin, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Illinois.

GRADUATE AND POSTGRADUATE COURSES, UNIVERSITY OF CALIFORNIA EXTENSION

Dr. Stacy R. Mettier, F.A.C.P., Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, Calif., announces the following program for 1954:

DIDACTIC RESIDENT COURSE IN OPHTHALMOLOGY, Part I, September, 1953 through January, 1954; Part II, January through May, 1954.

CARDIOVASCULAR DISEASES, February 1-5, mornings, at Medical Center.

ELECTROCARDIOGRAPHY, February 1-5, afternoons, at Medical Center.

DIAGNOSTIC EXFOLIATIVE CYTOLOGY FOR PHYSICIANS, February 8-19, all day, at Medical Center.

SYMPOSIUM ON HEART AND LUNG, February 19-21, week-end.

COURSE FOR GENERAL PRACTITIONERS, March 8-12, all day, at Mount Zion Hospital.

SYMPOSIUM ON EMERGENCIES: MEDICAL, SURGICAL, OBSTETRICAL, April 16-18, week-end.

COURSE IN INTERNAL MEDICINE, AMERICAN COLLEGE OF PHYSICIANS, June 14-18, all day.

CONFERENCE ON GENERAL SURGERY, September 13-17, all day, at Medical Center.

CONFERENCE ON FRACTURES AND DISEASES OF THE BONE, September 20-23, all day, at San Francisco County Hospital.

MEDICINE FOR GENERAL PRACTITIONERS, September 21 through December 7, Tuesday evenings, at East Oakland Hospital, Oakland.

EVENING LECTURES IN MEDICINE, Part I and Part II, September 16 through December 9, Thursday evenings, at Mills Memorial Hospital, San Mateo.

SYMPOSIUM ON ENDOCRINE DISEASES AND GERIATRICS, October 22-24, week-end.

UNIVERSITY OF CINCINNATI INSTITUTE OF INDUSTRIAL HEALTH
OFFERS FELLOWSHIPS

The Institute of Industrial Health of the University of Cincinnati will accept applications for a limited number of Fellowships in a graduate course of instruction in preparation for the practice of Industrial Medicine. Any registered physician who is a graduate of a Class A medical school and who has completed satisfactorily at least two years of training in an accredited hospital may apply. (Service in the Armed Forces or private practice may be substituted for one year of training.)

Instruction consists of a two-year period of intensive training in Industrial Medicine, followed by one year of practical experience under adequate supervision in industry. Candidates satisfactorily completing the course will be awarded the degree of Doctor of Industrial Medicine. During the first two years, stipends for the Fellowship vary from \$2,100 to \$2,700 in the first year and \$2,400 to \$3,000 in the second year, according to the marital status of the individual. In the third year the candidate will be compensated for his service by the industry in which he is completing his training. A one-year course, without stipend, is also offered to qualified applicants.

Requests for additional information should be addressed to the Institute of Industrial Health, College of Medicine, Eden and Bethesda, Cincinnati 19, Ohio.

SECOND POSTGRADUATE COURSE BY AMERICAN DIABETES ASSOCIATION

A course in "Diabetes and Basic Metabolic Problems" will be given under the auspices of the American Diabetes Association at the Mayo Clinic and Mayo Founda-

tion, Rochester, Minn., Jan. 18-20, 1954, under the direction of Dr. E. H. Ryncarson, F.A.C.P., and Dr. Randall G. Sprague, F.A.C.P. Many members of the faculty are Fellows of the American College of Physicians. Dr. Edward L. Bortz, F.A.C.P., Philadelphia, is the Chairman of the Association's Committee on Professional Education. The registration fee is \$40.00 for members of the Association; \$75.00 for non-members. Full details of the course may be obtained through the Association office at 11 W. 42nd St., New York 36, N. Y.

INTERNATIONAL CONGRESS OF INTERNAL MEDICINE
TO BE HELD IN STOCKHOLM IN SEPTEMBER

The Third International Congress of Internal Medicine will be held in Stockholm, Sept. 15-18, 1954, under the auspices of the International Society of Internal Medicine, in which forty nations are represented. The program for the Congress includes two symposia, one dealing with hypertension, its pathogenesis and treatment, and the other with collagen diseases. Several American specialists in internal medicine will be among the principal speakers. In addition, papers will be presented on such subjects as heart diseases, endocrine disturbances, gastro-intestinal diseases, and diseases of the blood and liver. The meetings will be held in the Stockholm Concert Hall. Visits will be made to hospitals and scientific institutions. The Congress Committee in Stockholm is headed by Professor Nanna Svartz, of the Caroline Medical Institute, who is President of the International Society of Internal Medicine.

FIFTH INTERNATIONAL CONGRESS ON MENTAL HEALTH

The Fifth International Congress on Mental Health and International Institute on Child Psychiatry will be held in Toronto, Can., Aug. 14-21, 1954. The theme of the Congress is "Mental Health in Public Affairs." Internationally known leaders in the mental health field will present papers of general interest at the Plenary Sessions. Papers presented at the Technical Sessions will deal with activities and progress in the various fields representing the broad mental health movement. The program is designed to interest lay people as well as workers in the various professional groups concerned with mental health programs and activities. Further details may be obtained from the Congress Office, 111 St. George St., Toronto, Can.

DR. FELIX JOEL UNDERWOOD RECEIVES LASKER AWARD

Dr. Felix Joel Underwood, F.A.C.P., Jackson, Miss., Executive Officer, Mississippi State Board of Health, was one of the recipients of the Lasker Awards bestowed during the 81st Meeting of the American Public Health Association in New York City, Nov. 12, 1953. Dr. Underwood received the award "for demonstrating how a well-founded, long-sustained and expanding pattern of public health services benefits the people. . . . Among his steady stream of accomplishments are county health units, child guidance clinics, programs for rural medical education, a new state medical school, and activities designed to control cancer and heart disease."

Regarded as one of the nation's top medical honors, the award consists of a purse of \$1,000, a hand-illuminated, leather-bound citation and a gold statuette of the Winged Victory, symbolizing the medical triumph over death and disease. The award is given by the Albert and Mary Lasker Foundation "for outstanding contributions in research relating to diseases which are major causes of death and disability, and for distinguished services in the field of public health."

Dr. Theodore G. Klumpp, F.A.C.P., New York City, has recently been appointed a member of the Task Force on Medical Services of the Commission on Organization of the Executive Branch of the Government, under the Chairmanship of former President Herbert Hoover. Other members of the Commission include the following Fellows of the College: Drs. Francis J. Braceland, Hartford, Conn., Hugh R. Leavell, Boston, Walter B. Martin, Norfolk, Va., J. Roscoe Miller, Chicago, and Dwight L. Wilbur, San Francisco, a Regent of the College. Objectives of the Medical Task Force are: to provide better medical care for beneficiaries of the Federal medical program; create a better foundation for training and medical service in Federal agencies; reduce the drain of doctors away from private practice; provide better organization for medical research, and to provide a better state of medical preparedness for war.

Dr. E. Cowles Andrus, F.A.C.P., Baltimore, President-Elect of the American Heart Association, is one of the recent appointees to the National Advisory Heart Council. The Council advises Dr. Leonard A. Scheele, The Surgeon General, U. S. Public Health Service, on matters concerning the operation of the National Heart Institute.

Maj. Wallis L. Craddock, (MC), USAR (Associate), Veterans Administration Hospital, Fort Douglas Station, Utah, received the Sir Henry Wellcome Award of the Association of Military Surgeons of the United States at the annual honors night dinner in Washington, D. C., Nov. 11, 1953. Maj. Craddock won the award for his essay entitled "An Evaluation of Pulmonary Features of Systemic Fungus Diseases."

Capt. Lloyd R. Newhouser, (MC), USN, F.A.C.P., Chief of the Professional Division, Bureau of Medicine and Surgery, shared the Gorgas Award for research work on blood and plasma substitutes during World War II with Col. Douglas B. Kendrick, (MC), USA, Surgeon of the United States Military Academy, West Point, N. Y.

At the October annual session of the Royal College of Physicians and Surgeons of Canada at Montreal, Dr. Edward S. Mills, F.A.C.P., Montreal, was elected a Vice President, representing the Medical Division. Dr. Mills is Physician-in-Chief and Director of the University Clinic at the Montreal General Hospital and Professor of Medicine at McGill University.

Dr. Richard N. O'Dell (Associate), Charleston, W. Va., was recently installed as President of the West Virginia Diabetes Association.

Dr. William Kaufman (Associate), Bridgeport, Conn., was elected President of the American Academy of Psychosomatic Medicine at a recent organizational meeting in New York. The purpose of the society is "to advance the scientific knowledge and practice of those aspects of medicine which relate to the interaction of mind, body, and environment, by means of study, laboratory and clinical research, meetings, and discussions in coöperation with other workers in these and related fields."

In addition to Dr. Sigurd W. Johnsen, F.A.C.P., Passaic, N. J., who was installed as President of the National Gastroenterological Association at the recent annual meeting in Los Angeles, Dr. C. Wilmer Wirts, F.A.C.P., Philadelphia, was elected Third Vice President. Dr. Samuel Weiss, F.A.C.P., New York City, was reappointed Editor-in-Chief of *The Review of Gastroenterology*.

Col. James E. Ash, (MC), USA, Retired, F.A.C.P., Washington, D.C., was the recipient of the Ward Burdick Award at the annual meeting of the American Society of Clinical Pathologists, held in Chicago, Oct. 12-16, 1953. The gold medal, named after the first secretary of the Society, who died in office in 1928, is presented to that person who has made outstanding contributions to clinical pathology. Dr. Ash received the award in recognition of his work in establishing an educational program for tumor and tissue diagnosis.

Dr. Donald S. Smith, F.A.C.P., Pontiac, was recently elected President of the Michigan Allergy Society. Other officers are Dr. Joseph H. Shaffer, F.A.C.P., Detroit, Vice President, and Dr. Sidney Friedlaender, F.A.C.P., Detroit, Secretary-Treasurer.

Under the auspices of the Committee for Graduate Medical Education of the Alameda-Contra Costa Medical Association and the Institute for Metabolic Research of the Highland-Alameda County Hospital, "The Dynamics of Endocrine Disease," a graduate assembly designed to emphasize clinical physiology, diagnosis, and treatment, and to promote constructive discussion, will be held Feb. 8-13, 1954, in the Highland-Alameda County Hospital, Oakland, Calif. The program emphasizes such topics as "The Pituitary Gland," "Parathyroids," "Thyroid," "Carbohydrate Metabolism—Diabetes," "The Adrenals," and "The Gonads." Faculty members include Dr. Elmer Alpert (Associate), Rahway, N. J.; Dr. E. B. Astwood, F.A.C.P., Boston; Dr. Edgar S. Gordon, F.A.C.P., Madison, Wis.; Dr. Leela Craig, F.A.C.P., and Dr. Salvatore P. Lucia, F.A.C.P., San Francisco, and the following members of the hospital staff: Dr. Kenelm W. Benson, F.A.C.P., Dr. Laurance W. Kinsell, F.A.C.P., Dr. Thomas C. McCleave, Jr., F.A.C.P., and Dr. Hobart Rogers, F.A.C.P.

Dr. Oscar A. Sander, F.A.C.P., Milwaukee, Wis., served as Chairman of a joint medical-legal conference and of a conference on trends in industrial medicine at the Eighteenth Annual Meeting of the Industrial Hygiene Foundation, held in Pittsburgh, Pa., Nov. 18-19, 1953. Dr. Samuel T. Nicholson, Jr., F.A.C.P., Pottstown, Pa., and Dr. Edward M. Kline, F.A.C.P., Cleveland, respectively, led the discussions of "The Stress Disorders" and "Problems Associated with Older Workers."

Dr. S. O. Waife, F.A.C.P., Indianapolis, Ind., discussed "Nutrition and the Long Life" at the regular monthly meeting of the Kanawha Medical Society, which met Oct. 13 in Charleston, W. Va.

Dr. John Minor, F.A.C.P., College Governor for the District of Columbia, and Maj. Gen. George E. Armstrong, (MC), USA, F.A.C.P., The Surgeon General, were two of the principal speakers at the Eighth Annual Meeting of the Society of Medical Consultants to the Armed Forces, held at Walter Reed Army Medical Center, Nov. 23, 1953. President of the Society, Dr. Minor spoke from his experience as a consultant to the Army Surgeon General and discussed generally the rôle of consultants to the medical services of the Army, Navy, and Air Force.

Dr. Joseph F. Ross, F.A.C.P., Boston, discussed "The Blood Volume in Congestive Heart Failure" when he was a guest speaker at a joint meeting of the Chicago Medical Society and the Postgraduate Course in Cardiology and Hematology, held at the Sheraton Hotel, Nov. 12, 1953.

Dr. Monroe J. Romansky, F.A.C.P., Washington, D. C., presented a paper, "Antibiotics Other Than Penicillin in the Treatment of Syphilis," at the Antibiotics Symposium sponsored by the Department of Health, Education, and Welfare, held Oct. 28-30, 1953, in Washington.

Under the Presidency of Dr. Arthur E. T. Rogers (Associate), Costa Mesa, the California Sanatorium Association held its annual meeting, Nov. 9, 1953, at Redwood City. Dr. Harold G. Trimble, F.A.C.P., Oakland, spoke on "A Physician's Observations of European Sanatoria," and Dr. Edward Kupka, F.A.C.P., Berkeley, discussed "Developments in the Tuberculosis Program of the State Department of Public Health." Dr. H. Corwin Hinshaw, Sr., F.A.C.P., San Francisco, delivered the "Annual Report on Antimicrobial Therapy," and Dr. William A. Winn, F.A.C.P., Springville, was moderator of a panel discussion on "Adult Rehabilitation and Special Patient Services."

Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, addressed the New Haven (Conn.), Medical Society, Nov. 4, 1953, on "Recent Advances in the Present Status of Diabetes." Other speakers in the bi-weekly series of lectures have included Dr. Elmer Alpert (Associate), Rahway, N. J., whose topic on Dec. 2 was "Present Status of Cortisone and ACTH Therapy." Dr. Edwin B. Astwood, F.A.C.P., Boston, Mass., is speaking on "Advances of Metabolism of Pituitary Gland, Related Factors" on Jan. 20, 1954.

Speakers and their topics at a Postgraduate Teaching Day on Arthritis and Rheumatism, presented at the Rochester (N. Y.) Academy of Medicine, Nov. 12, 1953, were Dr. Charles A. Ragan, Jr., F.A.C.P., New York City—"Differential Diagnosis of Rheumatoid Arthritis"; Dr. Joseph Lee Hollander, F.A.C.P., Philadelphia—"Present-Day Treatment of Chronic Arthritis"; and Dr. Joseph J. Bunim, F.A.C.P., Bethesda, Md.—"Vascular Lesions in Rheumatoid Arthritis."

Guest speakers at the Seventeenth Annual Meeting of the New Orleans Graduate Medical Assembly, to be held March 8-11, 1954, will include Drs. Julian M. Ruffin, F.A.C.P., Durham, N. C. (Gastroenterology), Walter C. Alvarez, F.A.C.P., St. Paul, Minn. (Medicine), and William D. Stroud, F.A.C.P., Philadelphia (Medicine).

Dr. Herrman L. Blumgart, F.A.C.P., Boston, was among the guest speakers at the Fifth Annual Symposium on Heart-Disease, sponsored by the Washington State Heart Association and the Washington State Department of Health, held at the University of Washington Medical School, Seattle, Nov. 6-7, 1953.

Speaking on "Roentgen Diagnosis of Lesions of the Lung," Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, addressed the Fort Steuben Academy of Medicine, Steubenville, Ohio, on Nov. 10, 1953. Other members of the College who will participate in the series of monthly meetings include Dr. Harold Feil, F.A.C.P., Cleveland, who will discuss "Surgical Aspects of Heart Disease" on Feb. 9, 1954, and Dr. Charles A. Doan, F.A.C.P., Columbus, College Governor for Ohio and Chairman of the Board of Governors, whose topic, on May 11, will be "The Cytopenic State."

Dr. Carl V. Moore, F.A.C.P., St. Louis, College Governor for Missouri, was the guest speaker at a meeting of the Portland (Ore.) Academy of Medicine, held Nov. 5-6, 1953. His subjects were "Iron Metabolism and the Pathogenesis of Iron Deficiency Anemias" and "Platelets, Platelet Antibodies, Platelet Types and Thrombocytopenic Purpura."

At the annual meeting of the American Cancer Society in New York City, Nov. 3-4, 1953, Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, presented a paper on "Potential Application of Supervoltage Roentgen Rays in the Detection of Early Pulmonary Lesions," and Dr. Peter A. Herbut, F.A.C.P., Philadelphia, discussed "Practical Applications of Exfoliative Cytology in the Early Diagnosis of Lung Cancer."

At the annual meeting of The Association of Life Insurance Medical Directors in New York City, Oct. 14-16, 1953, Dr. Henry B. Kirkland, F.A.C.P., and Dr. Harry E. Ungerleider, F.A.C.P., both of New York, participated in a panel discussion on Systolic Heart Murmurs. Dr. J. Scott Butterworth, F.A.C.P., New York, discussed and demonstrated his method of recording and reproducing heart murmurs, using the Cambridge Educational Electronic Cardioscope. Dr. Thomas Hale Ham, F.A.C.P., Cleveland, presented a paper entitled "An Experiment in Medical Education," and Dr. George P. Robb, F.A.C.P., New York, talked on "What Happens to Men Disabled by Heart Disease."

Dr. George T. Harrell, Jr., F.A.C.P., Winston-Salem, N. C., delivered a lecture entitled "Myxedema" on Nov. 17, 1953, at the Boston City Hospital. On Dec. 8, Dr. William Dock, F.A.C.P., New York City, presented "Apical Localization of Pulmonary Tuberculosis." The lectures were part of the series sponsored by the Boston City Hospital House Officers' Association.

Among the guest speakers at the 23rd Annual Conference of the Oklahoma City Clinical Society, held Oct. 26-29, 1953, were Drs. W. Paul Holbrook, F.A.C.P., Tucson, Ariz.; George Piness, F.A.C.P., Los Angeles; William G. Leaman, Jr., F.A.C.P., and Perry S. MacNeal, F.A.C.P., Philadelphia.

Dr. O. A. Brines, F.A.C.P., Detroit, and Dr. Eugene P. Pendergrass, F.A.C.P., Philadelphia, are among the principal speakers at the Second Annual Cancer Seminar being presented Jan. 14-16, 1954, at Phoenix, Ariz. Dr. O. O. Williams (Associate), Phoenix, is among the Arizona physicians serving as moderators of panel discussions.

Dr. Herbert T. Kelly, F.A.C.P., Philadelphia, gave a paper entitled "Geriatric Aspects of Nutrition" before the Lackawanna County Medical Society in Scranton, Pa., Oct. 27, 1953.

"What Are the Issues in TB Control Today?" was the title of the talk delivered Nov. 13, 1953, by Dr. Harold A. Lyons, F.A.C.P., Associate Professor of Medicine at the State University of New York College of Medicine at New York City, when he addressed the annual meeting of the Brooklyn Tuberculosis and Health Association.

Dr. Robert A. Cooke, F.A.C.P., New York City, discussing "Bacterial Allergy," was the principal speaker at the sixth meeting of the New England Conference on Allergy and Related Subjects, held Dec. 2, 1953, in Boston.

Dr. Samuel M. Feinberg, F.A.C.P., Professor of Medicine and Director of the Allergy Research Laboratory, Northwestern University Medical School, Chicago, spoke on the subject of "Allergy to Chemotherapy" at Coronado, Calif., on Dec. 9, 1953, in a Symposium on Acute Infectious Diseases, sponsored by the California Academy of General Practice and the Lederle Laboratories. He was invited also to be the guest speaker on Dec. 10 at a seminar of the research staff of The Upjohn Company. His subject was "Allergy—Research Trends and Needs."

Dr. S. Spafford Ackerly, F.A.C.P., Louisville, Ky., was among the out-of-state speakers at the annual medical symposium sponsored by Duke University School of Medicine, Durham, N. C., Dec. 1-2, 1953.

Dr. William Dameshek, F.A.C.P., Boston, Director of the Blood Research Laboratory, New England Center Hospital, talked on "Polycythemia and Related Conditions" at the Montefiore Hospital for Chronic Diseases, New York City, Dec. 4, 1953.

Dr. Jerome W. Conn, F.A.C.P., Ann Arbor, Mich., was the guest speaker at a postgraduate course in endocrinology that preceded the meeting of the Texas Academy of Internal Medicine, Dec. 5-6, 1953, in Houston. The course, which emphasized the pituitary-adrenal aspects of endocrinology, was sponsored by the Academy in cooperation with the Baylor University College of Medicine. On Dec. 4, Dr. Edward W. Boland, F.A.C.P., Los Angeles, was guest speaker for the meeting of the Texas Rheumatism Association.

Dr. Arnold Z. Pfeffer (Associate), New York City, will be one of the guest speakers at the Fifth International Conference of Doctors in Alcoholics Anonymous, to be held in Akron, Ohio, May 14-16, 1954.

Col. Fred H. Mowrey, (MC), USA, F.A.C.P., formerly of Battle Creek, Mich., has recently been appointed Assistant Chief Medical Consultant to the Office of the Surgeon General, Washington, D. C. Col. Mowrey had previously spent three years at the Percy Jones Army Hospital in Battle Creek as Chief of the Medical Service.

Dr. Louis L. Perkel, F.A.C.P., Jersey City, N. J., was recently appointed Director of the Department of Gastroenterology at the Jersey City Medical Center. Dr. Perkel will also serve as Chairman of the Committee on Intern and Resident Training.

Dr. Stewart G. Wolf, Jr., F.A.C.P., Oklahoma City, Okla., has recently been awarded a prize of \$1,500 for his work on a book entitled "The Nose." The volume was published in 1950 in collaboration with Dr. Thomas H. Holmes.

Dr. Armistead D. Williams (Associate), formerly of Richmond, has recently succeeded Dr. Julian R. Beckwith, Sr., F.A.C.P., as Chief of the Medical Department of the Chesapeake and Ohio Hospital, Clifton Forge, Va.

Dr. Hugh H. Hussey, Jr., F.A.C.P., has recently been appointed as Head of the Department of Preventive Medicine and Public Health at Georgetown University School of Medicine, Washington, D. C. Dr. Hussey has been a member of the faculty at Georgetown since 1936.

Dr. Edward C. Reifenstein, Jr., F.A.C.P., Oklahoma City, Okla., has recently been named Director of Biological and Therapeutic Research for the Schering Corporation, Bloomfield, N. J. Dr. Reifenstein has been Director of the Oklahoma Medical Research Institute and Hospital in Oklahoma City for almost three years.

Dr. James A. Campbell (Associate), Chicago, has recently been reappointed to the faculty of the University of Illinois College of Medicine as Professor of Medicine. Director of Medical Service at Presbyterian Hospital, Dr. Campbell was formerly Dean and Professor of Medicine at Albany Medical College, Albany, N. Y.

Dr. George W. F. Rembert, F.A.C.P., Jackson, Miss., former Governor for Mississippi, has recently been made a member of the Fifty-Year Club of the Mississippi State Medical Association. Born in 1879, Dr. Rembert received his M.D. from Tulane University of Louisiana School of Medicine in 1903, and has been a Fellow of the College since 1922.

Dr. Paul W. Spear, F.A.C.P., Brooklyn, N. Y., has recently been promoted to Chief of Medical Service at the Veterans Administration Hospital, Brooklyn. Since January, 1951, Dr. Spear had been Acting Chief of Medical Service.

Dr. Alex M. Burgess, Sr., F.A.C.P., Providence, R. I., Second Vice President of the College, recently received an award of merit for his work in the field of brotherhood. Governor Roberts of Rhode Island made the presentation on behalf of the Jewish War Veterans. Dr. Burgess, a veteran of World War I, was Chairman of the Medical Teaching Mission to Germany in 1948. For the past several years he has been Area Medical Section Chief at the Veterans Administration for New England and New York and has served as Physician-in-Chief of three Providence hospitals.

Dr. Virgil P. Sydenstricker, M.A.C.P., Augusta, Ga., delivered a lecture entitled "The Impact of Vitamin Research on the Practice of Medicine" at the bicentenary celebration of the publication of Lind's "Treatise of the Scurvy." The paper was presented at the invitation of the Scottish Nutrition Society and the Royal College of Physicians of Edinburgh. Dr. Sydenstricker also delivered the Robert Campbell Memorial Lecture, at which time Queen's University of Belfast presented a medal to him. Professor of Medicine at the Medical College of Georgia, Dr. Sydenstricker has also been awarded the King's Medal by the United Kingdom.

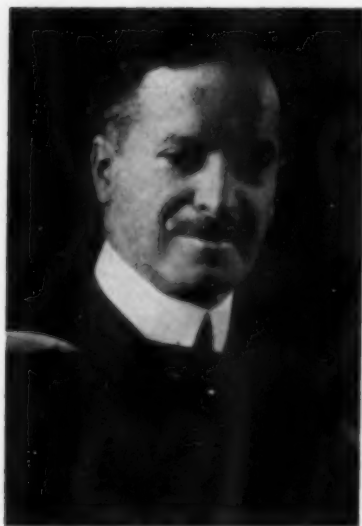
Dr. Walter Bauer, F.A.C.P., Boston, was one of the chief speakers at the annual meeting of the American Academy of Dermatology and Syphilology, held in Chicago, Dec. 5-10, 1953. The title of his lecture was "Some Facets of Medical Education."

Dr. T. K. Thomas, of St. George's Mission Hospital, calls attention to the great need of this hospital for medical books and journals, for the purchase of which funds are not available. Those interested may forward their donations to: St. George's Mission Hospital, Punalur P.O., Travancore, South India.

Dr. Howard R. Bierman, F.A.C.P., on September 15, 1953 assumed the position of Medical and Scientific Director of the Hospital for Tumors and Allied Diseases at the City of Hope Medical Center, Duarte, California. Dr. Bierman formerly was the Chief of the Clinical Section of the Laboratory of Experimental Oncology of the National Cancer Institute at Laguna Honda Home, San Francisco, and was an Associate Clinical Professor of Oncology at the University of California School of Medicine at San Francisco.

OBITUARIES

DR. CHARLES FERDINAND MARTIN



Dr. Charles Ferdinand Martin, B.A., M.D., C.M., LL.D. (Harvard, Queen's, McGill), D.C.L. (Bishop's), F.R.C.P. (C.), F.A.C.P., M.A.C.P., Montreal, Canada, sixth President of the American College of Physicians (1928-29), died at Montreal on October 28, 1953, at the age of eighty-five years. He was born in Montreal, October 14, 1868, and attended McGill University where he received his B.A. and M.D., C.M. degrees, the latter in 1892. Following graduation he was resident physician at the Montreal General Hospital, after which he proceeded abroad for a period of postgraduate study.

On his return in 1895 he became attached to the newly opened Royal Victoria Hospital and during the following years made outstanding contributions to medicine as a senior clinician in the hospital and an inspiring teacher on the Faculty of Medicine at McGill. In 1923 he became its Dean, and the following year gave up his consulting practice in order to devote full time to this office, the results of which

became evident in the reorganization of the preclinical departments, and a great expansion of the whole medical school, in which two outstanding events were the organization of the University Medical Clinic and the founding of the Montreal Neurological Institute.

Dr. Martin received the honorary degrees of D.C.L. from Bishop's College and LL.D from Queen's, Harvard, and McGill Universities. In June of 1953 the Canadian Medical Association paid him its highest tribute by bestowing on him the Frederick Newton Gisborne Starr Award. He was one of those actively concerned in the founding of the Royal College of Physicians and Surgeons of Canada, and was a charter Fellow. His activities as a member of the Canadian Medical Association are too many to enumerate here, but he was one of that gallant band who were responsible for the resuscitation of the Association in the precarious years of 1920-22 that has enabled it to grow to its present stature. In 1923 he was elected President, and in 1944 to Senior Membership.

One of his most noteworthy services was to the American College of Physicians in which he played a most important rôle in the reorganization of 1927-29. Perhaps his chief contribution was his extension of membership in the American College of Physicians among many distinguished leaders in the academic field, especially in the East. Through his leadership the Board of Regents designated Philadelphia as the permanent Headquarters of the College, the scientific features of its Annual Sessions were strengthened, and its official journal, *ANNALS OF INTERNAL MEDICINE*, was vastly improved. Dr. Martin adopted more adequate methods of determining the qualifications of candidates, and brought about the adoption of a proposal system eliminating the application plan theretofore in vogue. He initiated a special com-

mittee to study the finances of the College and a clarification of the By-Laws relating thereto. He promoted foresight and pre-planning in the administration of the College, and he coordinated the work of the Board of Governors and the Board of Regents. He instituted higher standards of admission and the enforcement of the presentation by candidates of adequate material, such as publications, theses, and evidences of professional growth. His contributions to the progress and development of the College were not confined to the period of his presidency, but extended over many succeeding years, his influence being perceptible throughout the length of his life. In 1940 he delivered the annual Convocational Oration, a fitting tribute on the occasion of the 25th anniversary of the founding of the College. During his active years in office there was a great impetus to the growth of the College membership, and the popularity of and respect for the College advanced significantly. He was recognized by the College not only with its presidency, but as a Master and as the first recipient of the Alfred Stengel Memorial Award for outstanding services.

Dr. Martin also made great contributions to the cultural life of Montreal, where following his retirement as Dean of Medicine, he devoted his energies and enthusiasms to the development of the Museum of Fine Arts and an increase in the educational and cultural phases of its activities that was reflected in the reawakening of public interest. In his earlier days he was a sports enthusiast, and won the Dominion Singles Tennis Championship in 1891 while a McGill student. He was also interested in fishing and golfing.

Surviving are his widow, the former Margaret Forrest Angus, and a sister, both of Montreal. His followers, admirers, and friends are legion throughout Canada, the United States, and the British Isles, all of whom will deeply miss his personal council, endearing friendship, inimitable smile and keen humor.

WALTER DE M. SCRIVER, M.D., F.A.C.P.,

Governor for the Province of Quebec

DR. O. VAN CALHOUN

O. Van Calhoun, M.D., F.A.C.P., was born in Birmingham, Iowa, on February 6, 1901, and died suddenly on November 2, 1953, in Lincoln, Nebr., the cause of death being coronary thrombosis. He was graduated from the Birmingham high school, where he had served as editor of the high school paper. He received his Bachelor of Science degree in 1926 from Iowa Wesleyan University and during the following year attended Johns Hopkins University, School of Public Health and Hygiene, as a graduate student. He received the degree of Doctor of Medicine in 1932 from Western Reserve University School of Medicine in Cleveland, Ohio, and served his internship at Lakeside Hospital in Cleveland.

Dr. Calhoun moved to Lincoln in 1934 and practiced here up to the time of his death. He was a member of the attending staff of Bryan Memorial and St. Elizabeth's Hospitals, Chairman of the Medical Section of Lincoln General Hospital and Chief of the Medical Service of the Veterans Administration Hospital in Lincoln. He was Adjunct Instructor in Medicine at the University of Nebraska College of Medicine. Last January he and three associates purchased the Olney Clinic Building and following remodeling, named it the Medical Arts Building of Lincoln. As a member of the Naval Reserve, he served as Lieutenant Commander in World War II at the San Diego Naval Hospital.

Dr. Calhoun became a Fellow of the American College of Physicians in 1942 and a Life Member in 1945. He was a member of the American Medical Association, Nebraska State Medical Association, Lancaster County Medical Society (Past President), Nebraska Heart Association (Board of Directors), and was a Diplomate of the American Board of Internal Medicine; member of the American Trudeau Society

(President of the Lancaster County Tuberculosis Association), American Rheumatism Society, and the American Heart Association. He was a former member of the Lincoln School Board, the Lincoln-Lancaster County Health Department (Past President), Board of Directors of the Lincoln Social Welfare Society and of the Lincoln Chamber of Commerce. His fraternities were Phi Delta Theta, Nu Sigma Nu, Sigma Xi and Gamma Alpha.

Active in many civic organizations and a favorite speaker, Dr. Calhoun had addressed many of these organizations as well as the graduating classes of schools of nursing in Lincoln. He had done extensive research work on heart disease and organized a heart clinic to acquaint laymen with facts about heart disease. He was a Mason, member of the Rotary Club, University Club, Country Club, Candlelight Club and S. Matthew's Episcopal Church.

As a collector of old and rare volumes, Dr. Calhoun had one of the finest private collections in the state, numbering several thousand medical books. He was particularly interested in the writings of Sir William Osler. He was an enthusiastic outdoor man, fisherman, hunter and a former college football player.

As may be seen from the foregoing, Dr. Calhoun was most active not only in the practice of medicine but in civic activities as well. He was an enthusiast of the first order and carried this enthusiasm with him throughout his many endeavors. He was most active in College affairs and down through the period of years, seldom missed attendance at regional and annual meetings. The passing of Dr. Calhoun has left a deep niche in the medical and civic affairs of his adopted city, Lincoln, Nebr.

JOSEPH D. MCCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

DR. A. D. CLOYD

Augustus David Cloyd, M.D., F.A.C.P., was born in Omaha, Nebr., on June 15, 1898, and passed away on November 9, 1953, following a prolonged and complicated cardiovascular illness. Dr. Cloyd became ill on December 27, 1952, and entered the hospital early in January, where he remained until his death.

Dr. Cloyd received the degree of Bachelor of Arts in 1920 from Amherst College and the degree of Doctor of Medicine in 1925 from the University of Nebraska College of Medicine. He served his internship at Cleveland City Hospital during 1925-1926, was a Fellow in Medicine during 1926-1927 and Assistant in the Division of Metabolic Diseases at Henry Ford Hospital during 1927-1928.

Immediately following his postgraduate study, Dr. Cloyd returned to Omaha and opened his office for the practice of medicine. He was appointed to the faculty of the University of Nebraska College of Medicine in the Department of Internal Medicine in 1934 and served until his last illness.

Dr. Cloyd was a member of the attending medical staff of the University of Nebraska, Bishop Clarkson Memorial and Immanuel Deaconess Hospitals, and a member of the courtesy staff of Creighton Memorial-St. Joseph's and Nebraska Methodist Hospitals. He served as President of the Immanuel Hospital staff during 1947-48.

Dr. Cloyd was elected to Fellowship in the American College of Physicians in 1941. However, from the time that he became an Associate he had attended postgraduate courses offered by the College annually from 1936 to 1939 and in 1941 and 1947. He was a Diplomate of the American Board of Internal Medicine.

Dr. Cloyd was a member of the American Medical Association, Nebraska State Medical Association, Omaha-Douglas County Medical Society (former member of the Executive Board), American Heart Association (scientific council), Omaha Clinical Club, and a Charter Member of the Omaha Mid-West Clinical Society.

Until recently Dr. Cloyd had been an avid flier and piloted his own plane to distant points from Omaha in his practice of medicine, including medical meetings, as well as for pleasure. He was a Wing Medical Officer in the Nebraska Civil Air Patrol and held the rank of Major. Among his other special interests was color photography.

Dr. Cloyd was an outstanding internist who faithfully adhered to the doctrines of the true physician in a quiet and unassuming fashion. He was held in high esteem by his confreres in Omaha and the surrounding territory.

JOSEPH D. MCCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

DR. JAMES H. DANGLADE

Dr. James Harold Dangle, F.A.C.P., Assistant Professor of Medicine at the University of Kansas School of Medicine, died on August 4, 1953, after an illness of about ten days.

Dr. Dangle was born in Webb City, Mo., on August 6, 1900. He was graduated from the University of Kansas School of Medicine in 1926, served his internship at that institution and then went to the Johns Hopkins Hospital for two more years of training as a member of the medical house staff. In 1929, he became Instructor in Medicine at the Johns Hopkins University School of Medicine. The following year, Dr. Dangle returned to Kansas City, was appointed to the faculty of his alma mater and began his career in the practice of internal medicine. From 1943 to 1946 he served as a Commander in the U. S. Naval Reserve, first in Cuba, and then as Chief of Medicine at the Naval Base in Norman, Okla. After his military duty had been completed, he resumed practice in Kansas City.

Dr. Dangle became recognized as one of the outstanding physicians of his community. He was held in high esteem by his medical colleagues as well as by his patients. He proved himself so fine a teacher that his advice and counsel were eagerly sought by younger members of the profession. His leadership was recognized by his appointment to the Executive Committee of St. Luke's Hospital and by his election to the Presidency of the Kansas City Academy of Medicine for 1937-1938. In addition to these honors, he became a Fellow of the American College of Physicians in 1940 and was a Diplomate of the American Board of Internal Medicine, a member of the Jackson County Medical Society, the Missouri State Medical Society, the American Medical Association and the Kansas City Southwest Clinical Society.

Dr. Dangle's premature death has been a severe loss to the community he served so well. He is survived by his wife, Mrs. Fern S. Dangle, and a son, James H. Dangle, Jr.

CARL V. MOORE, M.D., F.A.C.P.,
Governor for Missouri

DR. BENJAMIN E. GOODRICH

Benjamin Elmer Goodrich, M.D., F.A.C.P., died suddenly at his home in Pleasant Ridge, Mich., on June 15, 1953, at the age of 53, from an acute coronary occlusion. At the time of his death, Dr. Goodrich was in charge of the Respiratory Diseases Clinic of the Henry Ford Hospital, Detroit. He came to the hospital in 1926 as an interne after graduating from the State University of Iowa College of Medicine. He had served in two wars, as an infantryman in World War I and as a Navy medical officer during the North African and Sicily invasions of World War II, and he held a reserve commission as a Navy Captain.

He had been a Fellow of the American College of Physicians since 1942, a Fellow of the American College of Chest Physicians and a past President of its Michigan

Chapter, a member of the Central Society for Clinical Research, the American Trudeau Society, the Scientific Assembly of the American Heart Association, past President of the Henry Ford Hospital Medical Society, and a member of International Torch, a professional men's group. He belonged to Sigma Phi Epsilon, a social fraternity; Phi Beta Pi, a medical fraternity; and Sigma Xi, an honorary scientific fraternity.

At the time of his death, Dr. Goodrich was engaged in research for the Michigan Heart Association and had contributed many significant articles to medical literature on pulmonary and cardiac disease. He was well respected by his many friends in the medical profession and will be missed by all, but especially by the younger members of his hospital staff because of his intense interest in teaching, his sincerity in practice, and his philosophical approach to medicine.

Dr. Goodrich leaves a wife, Martha, and one son, Dr. Frank H. Goodrich, who is now serving as a Resident in Pathology at the Herman Keifer Hospital, Detroit.

H. M. POLLARD, M.D., F.A.C.P.,

Governor for Michigan

DR. LYNN T. HALL

Lynn Thompson Hall, M.D., F.A.C.P., of Omaha, Nebr., was born in Davenport, Iowa, July 10, 1887, and passed away on his 66th birthday, July 10, 1953, following a cerebral hemorrhage. He had been ill for about one year prior to his death and had retired from private practice in January, 1952.

Dr. Hall received the degree of Bachelor of Science in 1907 from Drake University and the degree of Doctor of Medicine in 1911 from Drake University College of Medicine and the State of Iowa College of Medicine. He interned at the Iowa Methodist Hospital, Des Moines, during 1911-1912 and took postgraduate work at Harvard University Graduate School of Medicine during 1912-1913, receiving a certificate in 1913. Immediately following this he moved to Omaha, where he practiced until the time of his death. The following year Dr. Hall was appointed to the faculty of the University of Nebraska College of Medicine as Assistant in Medicine. He served on the teaching staff, advancing in rank through the years, and in 1939 became Professor of Clinical Medicine. He was granted the rank of Professor Emeritus on June 1, 1952.

Dr. Hall was a member of the attending staff of the University of Nebraska, Nebraska Methodist, Bishop Clarkson Memorial and Lutheran Hospitals and a member of the courtesy staff of Immanuel Deaconess Institute and Creighton Memorial-St. Joseph's Hospital. He was a former member of the Drake University Board of Trustees. Dr. Hall had been a member of the medical staff of the Union Pacific Railroad since January, 1922, becoming Assistant Medical Director in 1943 and District Medical Officer in 1948. He retired from this position in November, 1952.

During World War I, Dr. Hall served with the 335th Omaha Ambulance Corps of the 84th Infantry Division and was Commanding Officer of Camp Hospitals No. 84 and No. 4 in France. He was separated from the service in 1920 with the rank of Captain.

Dr. Hall became a Fellow of the American College of Physicians in 1928 and a Diplomate of the American Board of Internal Medicine in 1928. He served as President of the Omaha-Douglas County Medical Society in 1951, and was a member of the Nebraska State Medical Association, the American Medical Association, a charter member of the Omaha Mid-West Clinical Society and a member of Sigma Alpha Upsilon, Phi Rho Sigma and Phi Beta Kappa fraternities.

Dr. Hall was a true physician. He gave liberally of his time to teaching, carrying on an active practice and directing the Medical Department of the Union

Pacific Railroad as well as devoting much time to medical society work and civic affairs. The people and the medical profession of Omaha have lost a true friend and a learned physician.

JOSEPH D. MCCARTHY, M.D., F.A.C.P.,
Governor for Nebraska

DR. FRED W. HARRIS

Dr. Fred William Harris, F.A.C.P., of Little Rock, Ark., died August 16, 1953, at the age of 55 years, of acute coronary thrombosis.

A native of Woodruff County, Ark., he was educated at Ouchita College and the University of Arkansas School of Medicine, where he was graduated in medicine in 1929. Dr. Harris interned at Touro Infirmary at New Orleans, later came back to Little Rock to join the staff at Trinity Hospital in 1930, where he remained until 1933 when he resigned to enter private practice in Little Rock.

He was a member of the Pulaski County Medical Society, Arkansas Medical Society, American Medical Association and Southern Medical Association; he had been a Fellow of the American College of Physicians since 1944 and was a Diplomate of the American Board of Internal Medicine as well as a member of the American Heart Association and the International Heart Congress.

Dr. Harris was an Associate Professor of Medicine at the University of Arkansas School of Medicine, and had helped to found the Arkansas Heart Association, formerly serving as its President. He contributed much to the promotion and dissemination of knowledge of heart disease vital to the laymen of Arkansas. For many years he was Medical Examiner for the children in the Arkansas School for the Deaf and the Arkansas School for the Blind. In this he acted in an advisory capacity on diet, activities and general health care. In this latter capacity he unselfishly donated many hours of his time and money to this institution.

Dr. Harris was a painstaking clinician and talented diagnostician, an outstanding and respected member of the medical profession in Arkansas, and his passing is a distinct loss to his community and to his state.

A. A. BLAIR, M.D., F.A.C.P.,
Governor for Arkansas

DR. WILLIAM RICHARDSON HOUSTON

Dr. William Richardson Houston, F.A.C.P., Austin, Texas, died August 31, 1953, three days after observing his eighty-first birthday.

Dr. Houston was the son of missionary parents and was born in 1872 in Hangchow, China. He received his M.A. degree in 1896 from Hampden-Sidney College and graduated in medicine in the Medical Department of the University of Georgia in 1902. He did postgraduate work at the University of Berlin in 1902-1903.

Dr. Houston was Clinical Professor of Medicine at the University of Georgia until 1935; he spent five years as Professor of Medicine at Yale-in-China and returned to the United States because of civil uprisings; he returned to the faculty of the University of Georgia. In 1935 Dr. Houston moved to Austin, Texas, where he was in practice for about five years. For some time he was Chief of Staff at Brackenridge Hospital, Austin, Texas.

In years gone by Dr. Houston was exceptionally active in attending the Annual Sessions of the College and engaging in College affairs. He served as Governor of the College for Georgia during the late 1920's.

He was a Diplomate of the American Board of Internal Medicine. At one time he was Vice Chairman of the Section on Medicine, American Medical Association; he was formerly Chairman of the Section on Medicine, Southern Medical Association

and he had been President and Secretary, Southern Interurban Clinical Club. At one time he was President of the Richmond County Medical Society of Georgia; he also served as President of the Travis County (Texas) Medical Society in 1939-1940. He was an honorary member of the Texas Internists Club. He became a Fellow of the American College of Physicians in 1928. He was author of "The Art of Treatment" (McMillan). Dr. Houston was recognized as a scholar and writer whose interests extended the breadth of medical science.

D. W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

DR. VICTOR MELTON LONGMIRE

Dr. Victor Melton Longmire, F.A.C.P., died July 27, 1953, of a myocardial infarction, at his home in Temple, Texas. He was born on November 2, 1889, in Glenfawn, Texas.

After graduation from Jacksonville College, Jacksonville, Texas, Dr. Longmire attended the University of Louisville School of Medicine, from which he received his medical degree in 1914. Since 1915 he had been associated with the Scott and White Hospital and Clinic in Temple, Texas, where, at the time of his death, he was Chief of the Medical Staff. His specialty was internal medicine. His postgraduate training had been at the Mayo Clinic, Jefferson Medical College Hospital, the Touro Infirmary and the New York Post-Graduate Hospital.

Dr. Longmire was a member of the American Medical Association; of the Texas Medical Association through the Bell County Medical Society. He was a life member of the American College of Physicians, having been elected a Fellow in 1926. He was secretary of the Section on Medicine and Diseases of Children of the Texas Medical Association in 1928, and he had served as secretary of the Bell County (Texas) Medical Society in 1938. He was a Diplomate of the American Board of Internal Medicine.

In World War I he was a first lieutenant in the Medical Corps of the United States Army. He served as an examining physician in the Selective Service System of the United States from October, 1940, to March, 1947.

He had been a Consultant in Medicine at the Gulf, Colorado and Santa Fe Hospital, Temple, Texas, since 1926.

Upon his death, the Board of Directors of the Scott and White Clinic, with which Dr. Longmire had been so long associated, adopted the following resolution:

"In the untimely death of Dr. V. M. Longmire on July 27, 1953, the Board of Directors of Scott and White Clinic has sustained an irreparable loss. In his death we have lost one of our most valuable associates, a fine physician, a wise counselor, a kindly man, and a dear friend. The Board desires to express its great appreciation of these qualities and enter upon the minutes this testimony to the memory of one we can ill afford to lose. His rare skill and understanding and the unselfishness which enhanced these attributes made a fundamental and lasting contribution to our institution and aided largely in developing better medical care for our patients."

D. W. CARTER, JR., M.D., F.A.C.P.,
Governor for Texas

DR. WILLIAM A. NORTHRIDGE

Dr. William Albert Northridge, F.A.C.P., died April 23, 1953, at the age of 93, being one of the oldest Fellows of the College. He was born in Brooklyn on July 27, 1860, attended the local public schools and the Polytechnic Institute of Brooklyn. He received his M.D. degree in 1882 from the Long Island College Hospital. There-

after he interned, 1882-84, at the Brooklyn Sea Side Home & Hospital, and remained at this institution as visiting physician and consulting physician. Later he was senior visiting pediatricist to St. Christopher's Hospital for Babies, Brooklyn, and then sometime during the 1920's he removed to San Diego, Calif., where he practiced pediatrics and internal medicine until approximately 1949, at which time he retired.

Dr. Northridge was former President of the Brooklyn Pediatrics Society, former Secretary of the Section on Pediatrics of the Kings County (N. Y.) Medical Society, and he was elected a Fellow of the American College of Physicians in 1920. He was the author of several published monographs and papers.

DR. ERWIN E. PETERS

Erwin E. Peters, B.S., M.D., a member of the staff of the Monroe Clinic at Monroe, Wisconsin, died suddenly from a cerebro-vascular accident on July 6, 1953, at the age of 42. He was born in New York City on December 19, 1910.

Dr. Peters received his doctorate in medicine from Cornell University Medical College in 1936 and then served as an intern and assistant resident at New York City Hospital until 1939. Then, after two years of post-graduate study at Johns Hopkins University School of Medicine, he enlisted in the Navy, serving at Brooklyn Naval Hospital, in Panama, at the Great Lakes Naval Station, and in New Guinea and Australia. He was discharged from the Navy in 1946 as a commander.

After a brief period of private practice in Forest Hills, New York, Dr. Peters went to Chicago as medical director of the Chicago Intensive Treatment Center. Postgraduate study was pursued further at the University of Minnesota Medical School and the Cook County Postgraduate School of Medicine. For a period of several years he was successively an instructor in medicine at Cornell University, Johns Hopkins University, Northwestern University and when he came to Wisconsin in 1948 he was appointed an associate preceptor in the Monroe Clinic unit of the University of Wisconsin Medical School. At the Clinic he devoted his time especially to dermatology and neurology. In the community he acted as a medical advisor for the Green County Chapter of the National Foundation for Infantile Paralysis.

Dr. Peters was a member of Alpha Omega Alpha, of the Green County Medical Society, the Wisconsin State Medical Society, and the American Medical Association. He was a diplomate to the American Board of Internal Medicine and in 1951 he became an Associate of the American College of Physicians.

Dr. Peters is survived by his widow, the former Ann Harris of Chicago, and two children, Erwin H., age 10, and Joan Carol, age 4.

KARVER L. PUESTOW, M.D., F.A.C.P.,
Governor for Wisconsin

DR. ANDREW S. ROBINSON

Dr. Andrew Smith Robinson, F.A.C.P., a member of the medical staff of the Goodyear Tire and Rubber Company since 1942, died on June 17, 1953, from bronchogenic carcinoma. Born in 1889, he received his medical degree from Western Reserve University School of Medicine in 1914, and was certified by the American Board of Internal Medicine in 1937.

He became a Fellow of the American College of Physicians in 1926, and for many years prior to his association with Goodyear, he practiced Internal Medicine in Akron, Ohio.

Dr. Robinson served with the British Army Medical Corps during World War I. He was held as a German prisoner for a considerable period of time, before release at the conclusion of hostilities.

Dr. Robinson continued as a Medical Consultant in the several Akron hospitals until the time of his death. He was a good companion, a courteous gentleman of high professional stature and of impeccable integrity.

His colleagues in Akron and the Ohio Fellowship of the American College of Physicians in particular, will miss, with his surviving family, the personal and professional fellowship which meant so much to Dr. Robinson.

CHARLES A. DOAN, M.D., F.A.C.P.,
Governor for Ohio

DR. CONLEY HALL SANFORD

Dr. Conley Hall Sanford, F.A.C.P., a source of inspiration and encouragement to many young physicians who through the years have earned prominence in Memphis and Mid-South medical cities, died November 16, 1953, at his home in Whitehaven. He was 60.

Dr. Sanford, who was equally prominent as a teacher and as a specialist in internal medicine, retired recently as chief of staff at John Gaston Hospital and chief of the Division of Medicine of the University of Tennessee College of Medicine.

Dr. Sanford had served as chief of staff and chief of the Division of Medicine here for 14 years when his retirement was announced October 4. Illness had prevented him from being at his office in the Physicians and Surgeons Building since August.

The eminent physician was born in Yorkville, near Dyer, Tenn. He attended public school in Henderson, and later was graduated from Freed-Hardeman College there. Other pre-medical training followed at Valparaiso University in Valparaiso, Ind. In 1918 he was graduated with honors from the University of Tennessee College of Medicine. He later interned at the Philadelphia (Pa.) General Hospital. He did postgraduate work in medicine in Vienna in 1927.

Dr. Sanford served with the Navy Medical Corps at the Naval Hospital at Charleston, S. C., during World War I. He joined the staff of the College of Medicine in 1920 as an assistant. He was made chief of the staff and chief of the Division of Medicine in 1939, succeeding the late Dr. J. B. McElroy. He was associated in private practice with Dr. Charles Deere and his nephew, Dr. Hall Tacket.

Dr. Sanford's achievements brought him charter membership in the local chapter of Alpha Omega Alpha, national honorary medical fraternity. He also was a charter member of the American Board of Internal Medicine and Tennessee Governor of the American College of Physicians. He was a member of the American Medical Association, the Memphis and Shelby County Medical Association and the Southern Medical Association. He was a member of the Whitehaven Kiwanis Club and Calvary Episcopal Church.

Dr. Sanford's wife, the former Mary Elizabeth Henderson, died three years ago. He leaves a son, Joe Sanford, a daughter, Miss Sallie Sanford, and three sisters, Mrs. J. O. Tacket and Mrs. L. C. Draper of Memphis, and Mrs. E. C. Sellers of McKenzie, Ala.

WILLIAM C. CHANEY, M.D., F.A.C.P.,
3rd Vice President, ACP



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with ductal distention.

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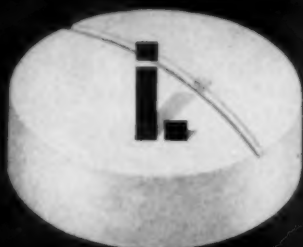
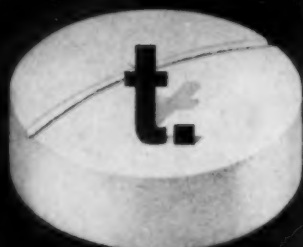
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1. Irvin, J. L.: The Secretion and Enterohepatic Circulation of Bile Acids; Replacement of Bile Acids in Biliary Insufficiency, North Carolina M. J. 13:206 (April) 1952.

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tell an electrocardiograph

by its record

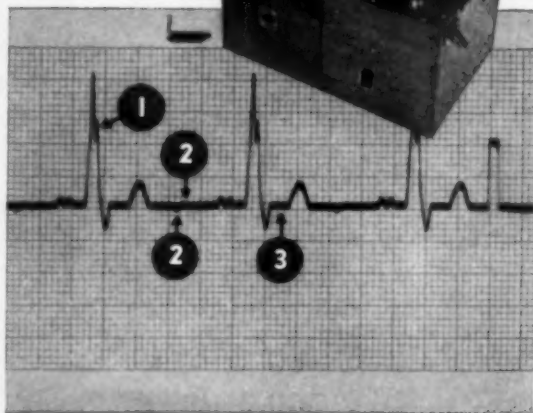
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of fresh gastric tissue		Pyridoxine HCl (B ₆)	0.2 mg.

Suggested Dosage: Adults: 1 to 2 teaspoonfuls. Children: ½ to 1 teaspoonful. Three times daily, or more as required. Preferably taken with food.
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Gastric mucosa (dried)	100.0 mg.	Thiamine HCl (B ₁)	10.0 mg.
		Vitamin C (ascorbic acid)	50.0 mg.

Suggested Dosage: 1 or 2 capsules three times daily, or as directed by the physician.
Preferably taken with food. No. 340 — Bottles of 100 and 1,000.



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of the effectiveness and low toxicity
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in treating bacterial urinary tract infections

is provided in its recent

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brand of nitrofurantoin



The N.N.R.
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on Furadantin
states:

“ Nitrofurantoin.—Furadantin (Eaton).—

Actions and Uses.—Nitrofurantoin, a nitrofuran derivative, exhibits a wide spectrum of antibacterial activity against both gram-positive and gram-negative micro-organisms. It is bacteriostatic and may be bactericidal to the majority of strains of *Escherichia coli*, *Micrococcus* (*Staphylococcus*) *pyogenes albus* and *aureus*, *Streptococcus pyogenes*, *Aerobacter aerogenes*, and *Paracolonobacterium* species. The drug is less effective against *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Alcaligenes faecalis*, and *Corynebacterium* species; many strains of these organisms may be resistant to it. However, bacterial resistance to other anti-infective agents is not usually accompanied by increase in resistance of the organisms to nitrofurantoin. The drug does not inhibit fungi or viruses.

Nitrofurantoin is useful by oral administration for the treatment of bacterial infections of the urinary tract and is indicated in pyelonephritis, pyelitis, and cystitis caused by bacteria sensitive to the drug. It is not intended to replace surgery when mechanical obstruction or stasis is present. Following oral administration, approximately 40% is excreted unchanged in the urine. The remainder is apparently catabolized by various body tissues into inactive, brownish compounds that may tint the urine. Only negligible amounts of the drug are recovered from the feces. Urinary excretion is sufficiently rapid to require administration of the drug at four to six hour intervals to maintain antibacterial concentration. The low oral dosage necessary to maintain an effective urinary concentration is not associated with detectable blood levels. The high solubility of nitrofurantoin, even in acid urine, and the low dosage required diminish the likelihood of crystalluria.

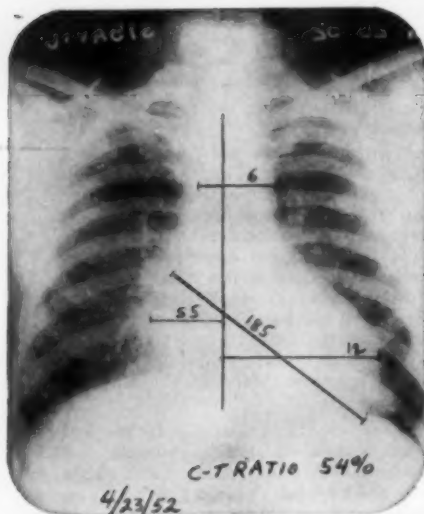
Nitrofurantoin has a low toxicity. With oral administration it occasionally produces nausea and emesis; however, these reactions may be obviated by slight reduction in dosage. An occasional case of sensitization has been noted, consisting of a diffuse erythematous maculopapular eruption of the skin. This has been readily controlled by discontinuing administration of the drug. Animal studies, using large doses administered over a prolonged period, have revealed a decrease in the maturation of spermatozoa, but this effect is reversible following discontinuance of the drug. Until more is known concerning its long-term effects, blood cell studies should be made during therapy. Frequent or prolonged treatment is not advised until the drug has received more widespread study. It is otherwise contraindicated in the presence of anuria, oliguria, or severe renal damage.

Dosage.—Nitrofurantoin is administered orally in an average total daily dosage of 5 to 8 mg. per kilogram (2.2 to 3.6 mg. per pound) of body weight. One-fourth of this amount is administered four times daily—with each meal and with food at bedtime to prevent or minimize nausea. For refractory infections such as *Proteus* and *Pseudomonas* species, total daily dosage may be increased to a maximum of 10 mg. per kilogram (4.5 mg. per pound) of body weight. If nausea is severe, the dosage may be reduced. Medication should be continued for at least three days after sterility of the urine is achieved.

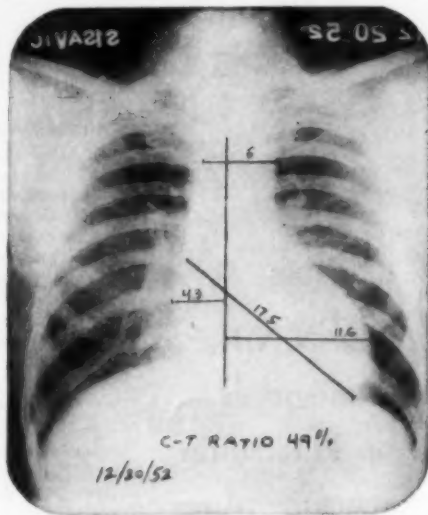
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Patient F.S. before Methium: Cardio-thoracic ratio 54%, blood pressure 240/160 mm. Hg.¹



After Methium: Cardio-thoracic ratio 49%, blood pressure 160/100 mm. Hg. This patient (F.S.) experienced no toxic side effects and did not lose a single day of work.¹

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In the first few months of therapy, over 80 per cent of the patients treated with oral hexamethonium have had gradual reduction in mean blood pressure of 20 mm. Hg or more.^{2,3} With continued treatment, up to or beyond a year, this reduction can often be maintained with no serious side effects and *no increase in dosage.*³

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1. Kuhn, P. H.: *Angiology* 4:195 (June) 1953.
2. Moyer, J. H.; Snyder, H. B.; Johnson, I.; Mills, L. C., and Miller, S. I.: *Am. J. M. Sc.* 225:379 (April) 1953.
3. Moyer, J. H.; Miller, S. I., and Ford, R. V.: *J.A.M.A.* 152:1121 (July 18) 1953.

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benefits

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It is universally acknowledged that the only effective means of weight reduction is restriction of caloric intake. Furthermore, it is acknowledged that no single food can be branded as fattening, that the solution to the problem is sensible limitation of the amounts of all foods eaten.

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This diet, a conventional reducing diet providing 1,200 to 1,400 calories

per day, allows a balanced variety of basic foods including bread. Note the sample menu.

Enriched bread is far more than just a carbohydrate food, as is often the mistaken concept. Moreover, in itself, it is not a "fattening food," since only the calorically excessive diet can induce increase in body weight. Three slices of enriched bread provide only 189 calories, yet this amount makes a worthwhile contribution of biologically applicable protein, B group vitamins, and valuable minerals including iron and calcium. Of even greater importance to the person dieting is the gustatory attractiveness which bread lends to the meal.



The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.

<p>BREAKFAST</p> <p>4 ounces tomato juice 1 boiled egg 1 teaspoon butter</p> <p>1 slice of toast Coffee with milk</p>	<p>LUNCH</p> <p>Liverwurst sandwich (1 ounce meat, mustard, lettuce) Celery Small bunch grapes 1 cup of milk</p>	<p>DINNER</p> <p>Roast chicken (3 slices, or 3 ounces) Broccoli Asparagus Tomato-cucumber saled, vinegar</p> <p>1 teaspoon butter Fresh fruit cup Coffee or tea with milk</p>	<p>BEDTIME</p> <p>Orange or $\frac{1}{2}$ banana $\frac{1}{2}$ cup milk</p>

AMERICAN BAKERS ASSOCIATION

20 North Wacker Drive

Chicago 6, Illinois



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THERAPY
WITH
POTENCY
THAT IS
MATHEMATICALLY
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achievement
in the
management of
hypertension*

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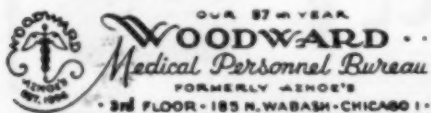


You Can't Be Twins—

But you can extend the benefits of your skill and experience without extending yourself beyond reasonable limits. Many other busy physicians have demonstrated the success of the plan which you, also, may desire to adopt; delegate some of your responsibilities to an associate whom you have (1) carefully selected; (2) proved competent by thorough induction into your methods.

The Woodward Bureau gives swift, systematic service in helping physicians to find associates who measure up. Many fine men in all fields of medicine announce their availability through our channels, and our background of over fifty years in professional placement has alerted us to careful interpretations of individual needs.

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w/penicillin

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Sulfamerazine.....	0.167 Gm.
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Sulfacetamide.....	0.111 Gm.

Tablets: Bottles of 100.

Suspension: Bottles of 4 and 16 oz.

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Sulfamerazine.....	0.167 Gm.
Sulfamethazine.....	0.056 Gm.
Sulfacetamide.....	0.111 Gm.

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Powder: In 60 cc. vials to provide 2 oz. of suspension by the addition of 40 cc. of water.

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from theophylline, ephedrine, phenobarbital, contained in tablet core

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